INHIBITOR OF COX

Background of the Invention

Field of the Invention

This invention relates to new compounds and pharmaceutically acceptable salts thereof having pharmacological activity.

Description of the Related Art

Cyclooxygenase catalyzes early stage reaction of arachidonate cascade, which is very important for a living body. For example, this cascade synthesizes prostaglandins as autacoids. So, antagonists or agonists of cyclooxygenase can be expected as medicines for treatment and/or prevention of inflammatory conditions, and so on.

As this cyclooxygenase, the presence of two isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II), is known (Proc. Nat. Acad. Sci. USA, 88, pp.2692-2696 (1991)). COX-I is always expressed over whole body and participates the maintenance of biological function at various tissues. On the other hand, COX-II is not always expressed and is induced by tumor promoter, growth factor, cytokine, and the like.

Among the antagonist of COX, traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, pp.6610-6614 (1993), etc). So, the therapeutic use thereof can cause undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, pp.3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared.

However, it was also reported that those "selective COX-II inhibitors" show some side-effects on kidney and/or insufficient efficacy on acute pains. Therefore, some compounds such as SC-560, mofezolac, etc., which have certain selective inhibiting activity against COX-I, have been researched.

WO98/57910 also shows some compounds having such selective activity. However, their selectivity of inhibiting COX-I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

And, WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. WO99/51580 shows some triazole derivatives having an inhibiting activity of cytokine production, and WO03/040110 shows some triazole derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity.

Further, WO92/21664, WO92/21665 and US4,051,250 show oxazole derivatives having anti/inframmatory activity.

However, the compounds described in WO92/21664 and WO92/21665 have necessarily hydroxylamino group in their structure and the compouns described in US4,051,250 have alkyl thio group substituted by carboxy, ester, $-CONH_2$ or CN group.

Brief Summary of the Invention

As a result of studies on the synthesis of new compounds and their pharmaceutical activity, the inventors of this invention have found that the new compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity). So, this invention relates to new compounds, which have pharmaceutical activity such as COX inhibiting activity, to a medicament and a pharmaceutical composition containing the new compounds.

Accordingly, one object of this invention is to provide the new compounds, a method for producing the same, a medicament and a pharmaceutical composition, which have a COX inhibiting activity

(especially, COX-I inhibiting activity).

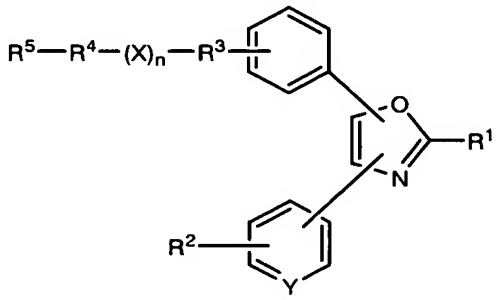
Another object of this invention is to provide a method for treatment and/or prevention of the diseases or conditions associated with COX and the new compounds for use as medicament in the treatment and/or prevention of the diseases or conditions associated with COX.

A further object of this invention is to provide a use of the new compounds for treating or preventing the diseases or conditions, and a use of the compounds for manufacturing a medicament for treating or preventing the diseases or conditions.

A further object of this invention is to provide an analgesic agent comprising the new compounds which is usable for treating and/or preventing the diseases or conditions.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

The new compounds of this invention can be represented by the following general formula (I):



(I)

wherein

R^1 is hydrogen, (lower)alkyl, (lower)alkyl substituted with substituent(s) (i) described later, (lower)alkenyl, (lower)alkynyl, cycloalkyl, aryl, saturated heterocyclyl, heteroaryl, (lower)alkoxy, (lower)alkoxy substituted with substituent(s) (i) described later, (lower)alkenyloxy, (lower)alkynyloxy, cycloalkyloxy, aryloxy, heteroaryloxy, (saturated heterocyclyl)oxy, amino, [(lower)alkyl]amino, di[(lower)alkyl]amino, di[(lower)alkyl]amino substituted with substituent(s) (i) described later on

(lower)alkyl, [(lower)acyl]amino, cycloalkylamino, arylamino, (saturated heterocyclyl)amino, heteroarylamino, carbamoyl, carbamoyl substituted with substituent(s) (ii) described later, (lower)acyl, cycloalkylcarbonyl, arylcarbonyl, (saturated heterocyclyl)carbonyl, heteroarylcarbonyl, [(lower)alkoxy]carbonyl, [(lower)alkyl]thio, [(lower)alkyl]thio substituted with substituent(s) (i) described later, [(lower)alkyl]sulfinyl, [(lower)alkyl]sulfonyl, cyano, carboxy, hydroxy, mercapto or halogen;

R^2 is (lower)alkyl, saturated heterocyclyl, (lower)alkoxy or cyano;

R^3 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^4 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^5 is hydrogen, (lower)alkyl, aryl, heteroaryl, (lower)alkoxy, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, [tri(lower)alkyl]silyloxy, amino, [(lower)alkyl]amino, di[(lower)alkyl]amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, [(lower)alkyl]sulfonylamino, heteroarylthiocarbonylamino, carbamoylamino, carbamoylamino substituted with substituent(s) (ii) described later on carbamoyl, aryloxycarbonylamino (which may be substituted with substituent(s) (iii) described later on aryl), [(lower)alkoxy]carbonyl, hydroxy, cyano or azido;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

n is 0 or 1;

substituent(s) (i) is(are) selected from the group consisting of (lower)alkyl, cycloalkyl, aryl, heteroaryl, (lower)alkoxy, [(lower)acyl]oxy, aryl[(lower)alkyl]oxy, [(lower)alkyl]sulfonyloxy, amino, [(lower)alkyl]amino, di[(lower)alkyl]amino, [(lower)acyl]amino,

carbamoylamino, [(lower)alkylcarbamoyl]amino, [di(lower)alkylcarbamoyl]amino, [(lower)alkoxycarbonyl]amino, [(lower)alkoxy]carbonyl, [(lower)alkyl]thio, arylthio, heteroarylthio, carboxy, hydroxy, hydroxyimino and halogen;

substituent(s) (ii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkyl substituted with hydroxy, (lower)alkyl substituted with carbamoyl, (lower)alkyl substituted with (lower)alkoxy, (lower)alkoxy, amino, [(lower)alkyl]amino and di[(lower)alkyl]amino;

substituent(s) (iii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, nitro and cyano;

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of this specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isoamyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "(lower)alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double bond between two carbon atoms, such as ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, and the like, and it is preferably (C2-C4)alkenyl, more preferably (C2-C3)alkenyl.

The "(lower)alkynyl" means a straight or branched chain aliphatic hydrocarbon having more than one triple bond between two carbon atoms, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like, and it is preferably (C2-C4)alkynyl, more preferably (C2-C3)alkynyl.

The "cycloalkyl" means (C3-C10)cycloalkyl group, such as

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably (C3-C6)cycloalkyl, more preferably (C3-C5)cycloalkyl, most preferably cyclopropyl.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphtyl, indenyl, or the like, and it is preferably (C6-C10)aryl, more preferably phenyl.

The "saturated heterocyclyl" means 5- or 6-membered saturated heterocyclyl group which contains at least one hetero atom such as nitrogen, oxygen, or sulfur atom. And the "saturated heterocyclyl" may be substituted with general substituent such as (lower)alkyl. The "saturated heterocyclyl" may include 5-membered saturated heterocyclyl group such as pyrrolidinyl, methylpyrrolidinyl, imidazolidinyl, pyrazolidyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidyl, isoxazolidyl, thiazolidyl, isothiazolidyl, or the like; and 6-membered saturated heterocyclyl group such as piperidyl, piperazinyl, tetrahydropyranyl, pentamethylene sulfide, morpholinyl, or the like.

The "heteroaryl" means 5-, 6-membered or condensed polycyclic aromatic heterocyclyl group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, tetrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, or the like; 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like; and condensed polycyclic heteroaryl group such as indolyl, isoindolyl, isoindole-1,3-dione-2-yl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, tetrahydroimidazo[1,2-a]pyrazine, or the like; and is preferably condensed polycyclic aromatic heterocyclic group, more preferably isoindole-1,3-dione-2-yl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, and the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "(lower)alkenyloxy" and "(lower)alkynyloxy" mean oxy group subsutituted with the above (lower)alkenyl and (lower)alkynyl, respectively. And "cycloalkyloxy", "aryloxy", "heteroaryloxy" and "(saturated heterocyclyl)oxy" mean oxy group subsutituted with the above cycloalkyl, aryl, heteroary and saturated heterocyclyl, respectively.

The "[(lower)alkyl]amino", "di[(lower)alkyl]amino", "cycloalkylamino", "arylamino", "(saturated heterocyclyl)amino" and "heteroarylamino" mean amino group subsutituted with the above one (lower)alkyl, two (lower)alkyls, cycloalkyl, aryl, saturated heterocyclyl and heteroaryl, respectively.

The "(lower)acyl" means a formyl and a (lower)alkyl carbonyl group, such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and the like, and it is preferably (C1-C4)acyl (including formyl), more preferably (C1-C2)acyl, most preferably acetyl.

The "[(lower)acyl]amino" means an amino group substituted with (lower)acyl group mentioned above, such as formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino, pivaloylamino, hexanoylamino, and the like, and it is preferably [(C1-C4)acyl]amino, more preferably [(C1-C2)acyl]amino, most preferably acetylamino.

The "cycloalkylcarbonyl", "arylcarbonyl", "(saturated heterocyclyl)carbonyl", "heteroarylcarbonyl" and "[(lower)alkoxy]carbonyl" mean carbonyl group substituted with the above cycloalkyl, aryl, saturated heterocyclyl, heteroaryl and (lower)alkoxy, respectively.

The "[(lower)alkyl]thio", "[(lower)alkyl]sulfinyl" and "[(lower)alkyl]sulfonyl" mean thio group, sulfinyl group and sulfonyl group substituted with the above (lower)alkyl, respectively.

The "(lower)alkylene" means a straight or branched chain aliphatic hydrocarbon divalent group, such as methylene, ethylene, propylene, methylethylene, butylene, methylpropylene, dimethylpropylene, pentylene, hexylene, and the like, and it is

preferably (C1-C4)alkylene, more preferably (C1-C3)alkylene, most preferably (C1-C2)alkylene.

The "(lower)alkenylene" means a straight or branched chain aliphatic hydrocarbon divalent group having more than one double bond between two carbon atom, such as ethenylene, propenylene, methylethenylene, butenylene, methylpropenylene, dimethylpropenylene, pentenylene, hexenylene, and the like, and it is preferably (C2-C4)alkenylne, more preferably (C2-C3)alkenylne.

The "[(lower)acyl]oxy" means an oxy group substituted with (lower)acyl group mentioned above, such as formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, and the like, and it is preferably (C1-C4)acyloxy, more preferably (C1-C2)acyloxy, most preferably acetyloxy.

The "[(lower)alkyl]sulfonyloxy" means a sulfonyloxy group substituted with (lower)alkyl group mentioned above, such as methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy, butanesulfonyloxy, hexanesulfonyloxy, and the like, and it is preferably [(C1-C4)alkyl]sulfonyloxy, more preferably [(C1-C2)alkyl]sulfonyloxy, most preferably methanesulfonyloxy.

The "[tri(lower)alkyl]silyloxy" means silyloxy group substituted with three (lower)alkyls mentioned above on silicon atom. The three (lower)alkyls may be the same or defferent each other. Such "[tri(lower)alkyl]silyloxy" includes trimethylsilyloxy and tert-butyldimethylsilyloxy, and it is preferably [(C1-C4)alkyl]silyloxy.

The "[(lower)alkoxy]carbonyl" means a [(lower)alkyl]-OCO- group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl, more preferably etoxycarbonyl.

The "[(lower)alkoxy]carbonylamino" means an amino group substituted with [(lower)alkoxy]carbonyl group mentioned above, such as methoxycarbonylamino, ethoxycarbonylamino,

propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, tert-butoxycarbonylamino, pentoxycarbonylamino, hexoxycarbonylamino, and the like, and it is preferably [(C1-C4)alkoxy]carbonylamino, more preferably tert-butoxycarbonylamino.

The "[(lower)alkyl]sulfonylamino" means a sulfonylamino group substituted on the sulfonyl group with (lower)alkyl group mentioned above, such as methanesulfonylamino, ethanesulfonylamino, propanesulfonylamino, butanesulfonylamino, hexanesulfonylamino, and the like, and it is preferably [(C1-C4)alkyl]sulfonylamino, more preferably [(C1-C2)alkyl]sulfonylamino, most preferably methanesulfonylamino.

The "heteroarylthiocarbonylamino" means an amino group substituted with heteroarylthiocarbonyl group, such as (5-membered heteroaryl)thiocarbonylamino such as pyrrolylthiocarbonylamino, imidazolylthiocarbonylamino, pyrazolylthiocarbonylamino, tetrazolylthiocarbonylamino, or the like; (6-membered heteroaryl)thiocarbonylamino; and (condensed polycyclic heteroaryl)thiocarbonylamino.

The "aryloxycarbonylamino" means an amino group substituted with aryloxycarbonyl group such as phenyloxycarbonylamino.

The "aryl[(lower)alkyl]oxy" means a (lower)alkoxy group substituted with aryl group mentioned above, such as benzyloxy, phenethyloxy, phenylpropyloxy, phenylbutyloxy, naphthylmethyloxy, or the like, and it is preferably aryl[(C1-C4)alkyl]oxy, more preferably aryl[(C1-C2)alkyl]oxy, more preferably phenyl[(C1-C2)alkyl]oxy, most preferably benzyloxy.

The "[(lower)alkylcarbamoyl]amino" means carbamoylamino group substituted with a (lower)alkyl group mentioned above on the nitorogen atom in the carbamoyl, such as methylcarbamoylamino, ethylcarbamoylamino, isopropylcarbamoylamino, tert-butylcarbamoylamino, and the like, and it is preferably [(C1-C4)alkylcarbamoyl]amino, more preferably [(C1-C2)alkylcarbamoyl]amino.

The "[di(lower)alkylcarbamoyl]amino" means carbamoylamino group substituted with two (lower)alkyl groups mentioned above on the nitorogen atom in the carbamoyl, such as dimethylcarbamoylamino, ethylmethylcarbamoylamino, diethylcarbamoylamino, and the like, and it is preferably [di(C1-C4)alkylcarbamoyl]amino, more preferably [di(C1-C2)alkylcarbamoyl]amino.

The "[(lower)alkoxycarbonyl]amino" means an amino group substituted with [(lower)alkoxy]carbonyl group mentioned above, such as methoxycarbonylamino, ethoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, and the like, and it is preferably [(C1-C4)alkoxy]carbonylamino.

The "arylthio" and "heteroarylthio" mean thio group subsutituted with the above aryl and heteroaryl, respectively.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a fluorine atom.

The (lower)alkyl, (lower)alkoxy, di[(lower)alkyl]amino and [(lower)alkyl]thio in the definition of R^1 may be substituted with substituent(s) (i). The carbamoyl in the definition of R^1 and carbamoylamino in the definition of R^5 may be substituted with substituent(s) (ii). And the aryloxycarbonylamino in the definition of R^5 may be substituted with substituent(s) (iii).

And the "(lower)alkyl substituted with hydroxy" may include hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 1-hydroxyisobutyl, 1-hydroxyisoamyl, and the like, and is preferably hydroxy(C1-C4)alkyl, more preferably hydroxy(C1-C2)alkyl.

The "(lower)alkyl substituted with carbamoyl" may include carbamoylmethyl, carbamoylethyl, carbamoylpropyl, carbamoylisopropyl, carbamoylisobutyl, carbamoylisoamyl, and the like, and is preferably carbamoyl(C1-C4)alkyl, more preferably carbamoyl(C1-C2)alkyl.

The "(lower)alkyl substituted with (lower)alkoxy" may include methoxymethyl, and the like, and is preferably (C1-C2)alkyl substituted with (C1-C2)alkoxy, more preferably methoxyethyl.

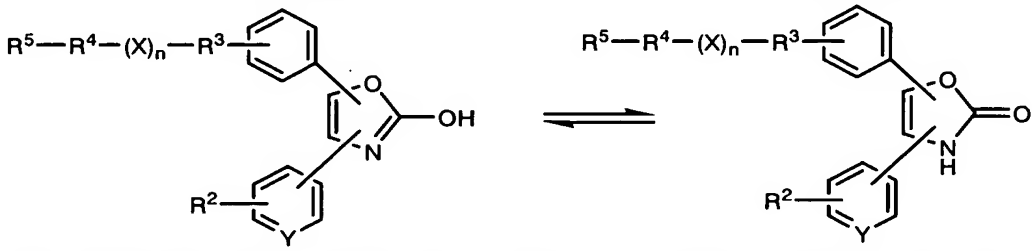
The "(lower)alkyl substituted with halogen" may include

fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, and the like, and is preferably (C1-C4)alkyl substituted with fluorine(s), more preferably (C1-C2)alkyl substituted with fluorine(s), more preferably methyl substituted with fluorine(s), most preferably difluoromethyl or trifluoromethyl.

In case of the number of "substituent(s) (i) to (iii)" are plural, they may be same or different each other. For example, R^1 may be hydroxy(phenyl)methyl.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers. For example, when R^1 is hydroxy, the compounds of the formula (I) may be tautomeric forms as follows.



In the scope of this invention, these tautameric forms are included.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

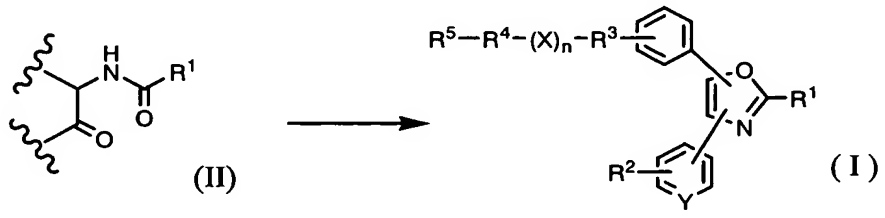
The new compounds of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and

include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

Detailed Description of the Invention

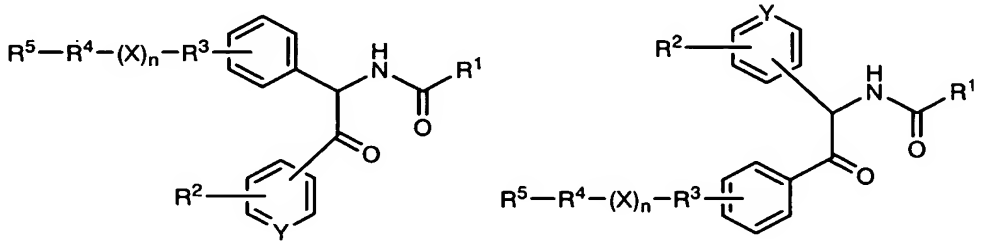
The compound of the formula (I) of the present invention can be prepared according to the following processes A-1 to A-3.

Process A-1



(II) (I)

In the above formula, R^1 to R^5, X, Y and "n" represent the same meanings as defined above. And Compound (II) may have either of following structure.



Hereinafter, this condition is the same with Compound (III), (IV), (VI) and (VII).

Process A-1 is the process for preparing Compound (I) from

Compound (II) by forming oxazole ring.

Compound (II) may be purchased if it is commercial, or synthesized according to Process B mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

As this process, two methods are mainly employable, which are one using phosphorus oxychloride ($POCl_3$) as condensation agent (A-1(1)) and the other using triphenylphosphine (A-1(2)).

Process A-1(1) is generally carried out by adding phosphorus oxychloride to the solution of Compound (II). The temperature at that time to be employable depends on the starting material, the solvent, etc., but it is usually room temperature. And after adding, the temperature is preferably raised to reflux.

The solvent employable in Process A-1(1) is not particularly limited so long as it is inactive in this reaction and dissolves moderately Compound (II) and phosphorus oxychloride. It may preferably include liquid hydrocarbon such as benzene, toluene.

The reaction time after adding phosphorus oxychloride depends on the starting material, the solvent, etc., but it is usually from 12hrs to 3days.

Process A-1(2) is generally carried out by adding the solution of triphenylphosphine, iodine and base (triethylamine, etc.) to the solution of Compound (II). The temperature at that time depends on the starting material, the solvent, etc., but it is usually room temperature.

The solvent employable in Process A-1(2) is not particularly limited so long as it is inactive in this reaction and can dissolve substrates moderately, and may preferably include halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride.

The reaction time after adding triphenylphosphine depends on the starting material, the solvent, etc., but it is usually from 12hrs to 3days.

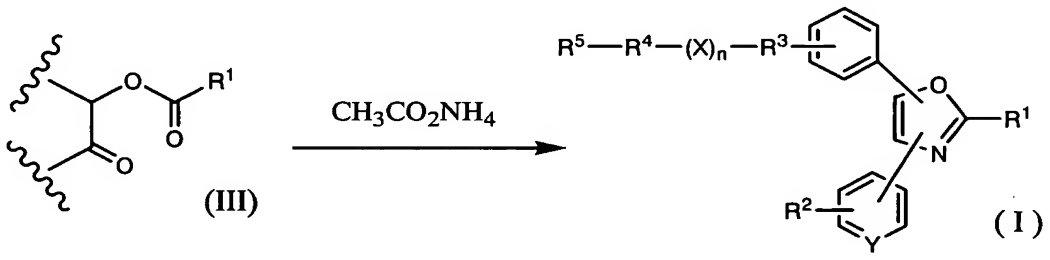
After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate,

chloroform, etc., and the organic layer is separated. The organic layer is washed by water, hydrochloric acid, saturated sodium hydrogencarbonate solution, brine, etc., dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc..

Which to be selected A-1(1) or A-1(2) in this process is mainly dependent on the property of R^1 group. So, either method of which yield is higher may be employed.

Compound (I) can be also synthesized by following Process A-2.

Process A-2



In the above formula, R^1 to R^5, X, Y and "n" represent the same meanings as defined above.

Process A-2 is the process for preparing Compound (I) from Compound (III) by forming oxazole ring besides Process A-1.

Compound (III) may be purchased if it is commercial, or synthesized according to Process C mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

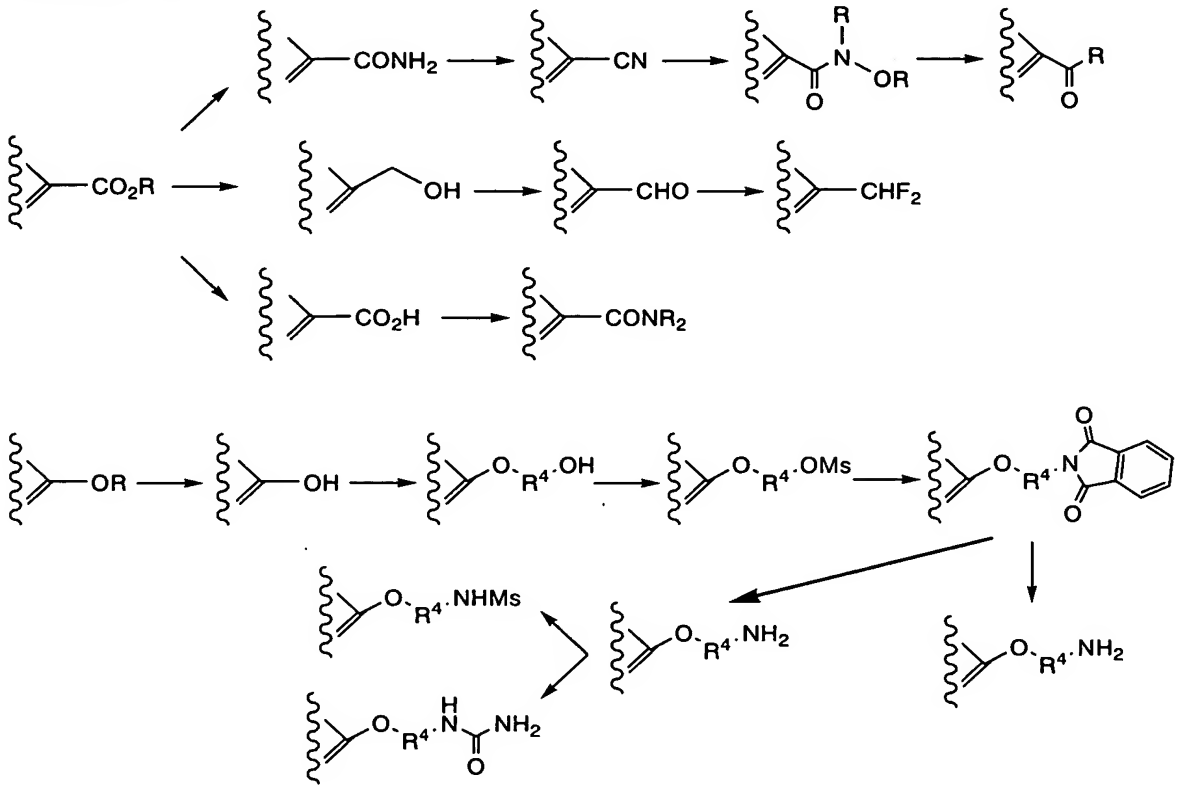
This process is generally carried out by adding ammonium acetate to the acetic acid solution of Compound (III). The temperature at that time depends on the starting material, the solvent, etc., but it is usually room temperature. And after adding ammonium acetate, the temperature is preferably raised to reflux.

The reaction time after adding ammonium acetate depends on the starting material, the solvent, etc., but it is usually from 30min to 12hrs, preferably from 1hr to 5hrs.

After the reaction, the solvent is removed in vacuo, and acetic acid is azeotropically removed with toluene, etc.. The residue is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and the organic layer is separated. The organic layer is washed by water, saturated sodium hydrogencarbonate solution, brine, etc., dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc..

Compound (I) can be transformed to the other Compound (I) by functional group trans formation, which is obvious to the person skilled in the organic chemistry. For example, first, Process A-1 or A-2 are carried out by using the compound which does not have reactive group as R^1 and the like, then, the R^1 and the like are transformed to reactive group. Some of such functional group trans formation reactions are illustrated as following Process A-3.

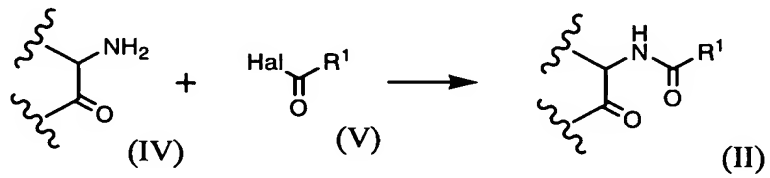
Process A-3



In the above formulae, R represents H, lower alkyl or aryl, which is not specified, and plural R may be same or different each other. "Ms" represents methanesulfonyl group. And R^4 represents the same meanings as defined above.

Compound (II), which is the starting compound of Process A-1, can be synthesized by following Process B.

Process B



(IV) (V) (II)

In the above formula, R^1 represents the same meanings as defined above. And "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process B is the process for preparing the Compound (II) by condensing Compound (IV) and (V).

Compound (IV) and (V) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds. But, in advance, Compound (V) can be synthesized from corresponding acid and pivaloyl chloride or oxallyl chloride, or the like, in one-pot. And corresponding acid anhydride may be also used as Compound (V).

This process is generally carried out by adding Compound (V) to the solution of Compound (IV). To accelerate the reaction, base such as pyridine may be added. The temperature at that time depends on the starting material, the solvent, etc., but it is usually 0℃ to room temperature. And after adding, the temperature may be raised to reflux.

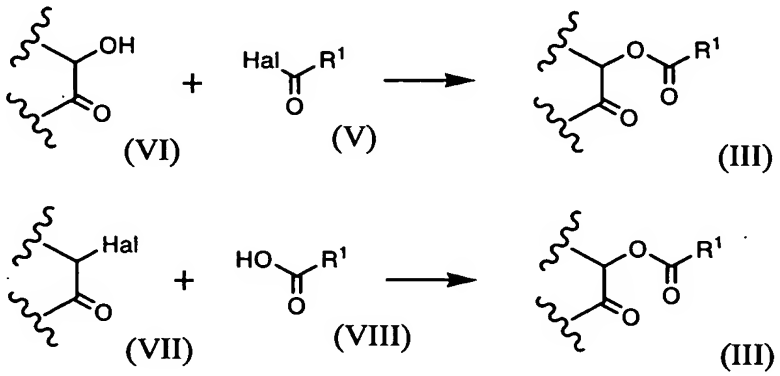
The solvent employable in Process B is not particularly limited so long as it is inactive in this reaction and dissolves moderately substrates, and may include preferably halogenated hydrocarbon such as dichloromethane, chloroform; liquid hydrocarbon such as benzene, toluene; ethers such as diisopropyl ether, tetrahydrofuran, dioxane.

The reaction time after the adding depends on the starting material, the solvent, etc., but it is usually from 1hr to 3days.

After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and the organic layer is separated. The organic layer is washed by water, hydrochloric acid, saturated sodium hydrogencarbonate solution, brine, etc., dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc.. However, the target compound may be used in next step (Process A-1) without purification.

Compound (III), which is the starting compound of Process A-2, can be synthesized by following Process C.

Process C



In the above formulae, R^1 and "Hal" represent the same meanings as defined above.

Process C is the process for preparing the Compound (III) in the presence of base.

Compound (V) to (VIII) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds, because their structure are comparatively simple.

The above two processes may be generally carried out by almost same condition, that is, by mixing base and Compound (V) and (VI) or Compound (VII) and (VIII) in solvent. The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually room temperature.

The solvent employable in Process C is not particularly limited so long as it is inactive in this reaction and dissolves moderately substrates, and may include preferably halogenated hydrocarbon such as dichloromethane, chloroform; ketone such as acetone, 2-butanone.

The base employable in this process for making basic condition is not particularly limited so long as it accelerates this reaction and may include alkali metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate; cesium carbonate; pyridine.

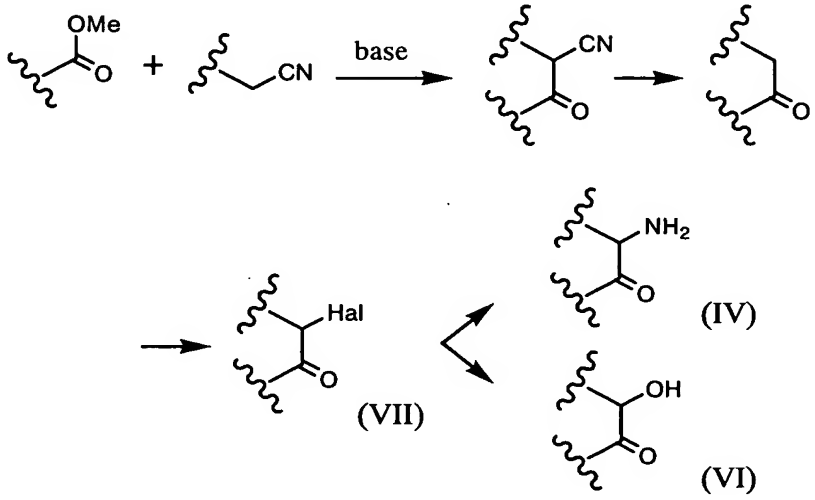
The reaction time depends on the starting material, the solvent, etc., but it is usually from 12hrs to 2days.

After the reaction, the mixture is partitioned between water and

organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and the organic layer is separated. The organic layer is washed by water, hydrochloric acid, saturated sodium hydrogencarbonate solution, brine, etc., dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc.. However, the target compound may be used in next step (Process A-2) without purification.

Compound (IV), (VI) and (VII) have comparably simple structure. So, these compounds can be synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds. For example, these compounds can be synthesized by referring following Process D.

Process D



Above Processes A to D, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

And above Processes A to D, compounds, which have reactive group, may be protected at the group on cue, and be deprotected on cue. In these reactions (protecting or deprotecting steps), concerning the kind of protective group and the condition of the reaction,

「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. (the contents of which are hereby incorporated by reference) may be referred.

The patents, patent applications and publications cited herein are incorporated by reference.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

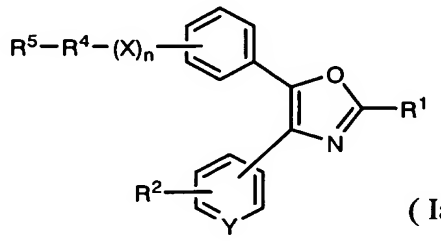
For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

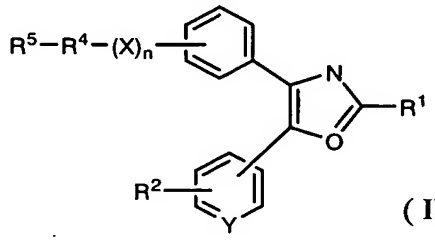
While the dosage of therapeutically effective amount of the compound (I) will depends on the age and condition of each individual patient, an average single dose of about 0.01mg, 0.1mg, 1mg, 10mg, 50mg, 100mg, 250mg, 500mg and 1000mg of the compound (I) may be

effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The compound (I) includes a compound of the formula (Ia) and (Ib), and is preferably compound of the formula (Ia):

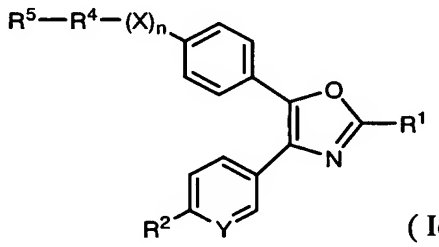


(Ia)

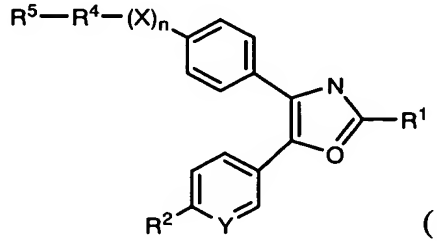


(Ib)

Additionally, the compound (I) includes compound of the formula (Ic) and (Id), and is preferably a compound of the formula (Ic):



(Ic)



(Id)

[in the above formulae, R^1 to R^5, X, Y and n represent the same meanings as defined above.]

And in the each definition of the compound formula(I), preferably,

(1) R^1 is hydrogen, (lower)alkyl, (lower)alkyl substituted with substituent(s) (i), cycloalkyl, heteroaryl, (lower)alkoxy, (lower)alkoxy substituted with substituent(s) (i), (lower)alkynyloxy, cycloalkyloxy, heteroaryloxy, di[(lower)alkyl]amino, di[(lower)alkyl]amino substituted with substituent(s) (i) on (lower)alkyl, [(lower)acyl]amino, heteroarylamino, carbamoyl, carbamoyl substituted with substituent(s) (ii), (lower)acyl, cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, [(lower)alkoxy]carbonyl,

[(lower)alkyl]thio, [(lower)alkyl]thio substituted with substituent(s) (i), [(lower)alkyl]sulfinyl, [(lower)alkyl]sulfonyl, cyano, carboxy or halogen,

(2) R^1 is (C1-C4)alkyl, (C1-C4)alkyl substituted with substituent(s) (i), cycloalkyl or heteroaryl,

(3) R^1 is (lower)alkyl substituted with halogen(s), or cycloalkyl,

(4) R^1 is (C1-C4)alkyl, or cycloalkyl,

(5) R^1 is (C1-C4)alkyl substituted with substituent(s) (i),

(6) R^1 is (C1-C4)alkoxy, (C1-C4)alkoxy substituted with substituent(s) (i), (C1-C4)alkynyloxy, (C3-C6)cycloalkyloxy or heteroaryloxy,

(7) R^1 is (C1-C4)alkoxy substituted with substituent(s) (i),

(8) R^1 is di[(C1-C4)alkyl]amino, di[(C1-C4)alkyl]amino substituted with substituent(s) (i) on (lower)alkyl, [(lower)acyl]amino or heteroarylamino,

(9) R^1 is di[(C1-C4)alkyl]amino substituted with substituent(s) (i),

(10) R^1 is carbamoyl substituted with substituent(s) (ii),

(11) R^1 is (lower)acyl,

(12) R^1 is [(lower)alkyl]thio substituted with substituent(s) (i),

(13) R^2 is (lower)alkoxy, or cyano,

(14) R^2 is (lower)alkoxy,

(15) R^2 is (C1-C4)alkoxy,

(16) R^3 is (lower)alkylene, or covalent bond,

(17) R^3 is (lower)alkylene,

(18) R^3 is (C1-C4)alkylene,

(19) R^3 is covalent bond,

(20) R^4 is (lower)alkylene, or covalent bond,

(21) R^4 is (lower)alkylene,

(22) R^4 is (C1-C4)alkylene,

(23) R^4 is covalent bond,

(24) R^5 is hydrogen, aryl, heteroaryl, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, [tri(lower)alkyl]silyloxy, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, carbamoylamino substituted with substituent(s) (ii) on carbamoyl,

[(lower)alkyl]sulfonylamino, [(lower)alkoxy]carbonyl, aryloxycarbonylamino (which may be substituted with substituent(s) (iii) on aryl), hydroxy, cyano or azido,

(25) R^5 is hydrogen,

(26) R^5 is aryl or heteroaryl,

(27) R^5 is [(C1-C4)alkyl]sulfonyloxy or [tri(C1-C4)alkyl]silyloxy,

(28) R^5 is amino,

(29) R^5 is carbamoylamino or carbamoylamino substituted with substituent(s) (ii) on carbamoyl,

(30) R^5 is carbamoylamino substituted with substituent(s) (ii) on carbamoyl,

(31) R^5 is aryloxycarbonylamino (which may be substituted with substituent(s) (iii) on aryl),

(32) R^5 is [(lower)alkyl]sulfonylamino, carbamoylamino or hydroxy,

(33) R^5 is hydroxy,

(34) X is "O", or "S",

(35) X is "O",

(36) X is "SO", or "SO_2",

(37) Y is "CH",

(38) Y is "N",

(39) n is 0,

(40) n is 1,

(41) substituent(s) (i) is(are) selected from the group consisting of (lower)alkyl, cycloalkyl, (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, di[(lower)alkyl]amino, [di(lower)alkylcarbamoyl]amino, heteroarylthio, hydroxy, hydroxyimino and halogen,

(42) substituent(s) (i) is(are) selected from the group consisting of (lower)alkyl and cycloalkyl,

(43) substituent(s) (i) is(are) selected from the group consisting cycloalkyl and hydroxyimino,

(44) substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy,

(45) substituent(s) (i) is(are) selected from the group consisting

of di[(lower)alkyl]amino and [di(lower)alkylcarbamoyl]amino,

(46) substituent(s) (i) is heteroarylthio,

(47) substituent(s) (i) is(are) selected from the group consisting of hydroxy and halogen,

(48) substituents (ii) is(are) selected from the group consisting of (lower)alkyl and (lower)alkoxy,

(49) substituents (ii) is(are) selected from the group consisting of (lower)alkyl substituted with hydroxy, (lower)alkyl substituted with carbamoyl and (lower)alkyl substituted with (lower)alkoxy,

(50) substituents (ii) is(are) selected from the group consisting of amino and di[(lower)alkyl]amino,

(51) substituent(s) (iii) is(are) selected from the group consisting of nitro and cyano,

(52) provided that R^5 is not hydrogen, when both of R^3 and R^4 are covalent bond and n is 0.

Preferred compounds of formula (I) may include

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol,

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol,

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide,

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea,

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol and

N-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide.

Examples

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1-1

Ethyl {[1,2-bis(4-methoxyphenyl)-2-oxoethyl]amino}- (oxo)acetate

To a suspension of 2-amino-1,2-bis(4-methoxyphenyl)ethanone hydrochloride (1.0g, 3.25mmol) in benzene (10mL) was added ethyl chlorooxoacetate (532mg, 3.90mmol) at room temperature and the mixture was heated to reflux with stirring for 2days.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound (1.25g, 103.6%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.37(3H, t, J=7.5Hz), 3.75(3H, s), 3.83(3H, s), 4.34(2H, q, J=7.5Hz), 6.42(1H, d, J=7.5Hz), 6.83(2H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 7.95(2H, d, J=8Hz), 8.49(1H, d, J=7.5Hz).

MS (ES+) : 372.14.

Example 1-2

Ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2- carboxylate

To a solution of ethyl {[1,2-bis(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 1-1 (1.25g, 3.37mmol) in benzene (15mL) was added phosphorus oxychloride (1.55g, 10.1mmol) at room temperature and the mixture was heated to reflux with stirring for 18hrs.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (909mg, 76.4%) as a pale yellow powder.

MP : 95-97℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.46(3H, t, J=7.5Hz), 3.84(3H, s), 3.85(3H, s), 4.51(2H, q, J=7.5Hz), 6.91(4H, d-like, J=8Hz), 7.58-7.62(4H, m).

MS (ES+) : 354.10.

Example 2

4,5-Bis(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

A mixture of ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 1-2 (400mg, 1.13mmol) and sodium methoxide (183mg, 3.40mmol) in formamide (4mL) was stirred at 100℃ for 2hrs.

After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with isopropyl ether to give the title compound (264mg, 71.9%) as a pale yellow powder.

MP : 133-135℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.79(3H, s), 3.81(3H, s), 7.00(2H, d, J=8Hz), 7.05(2H, d, J=8Hz), 7.52(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.93(1H, br-s), 8.30(1H, br-s).

MS (ES+) : 325.10.

Example 3

4,5-Bis(4-methoxyphenyl)-1,3-oxazole-2-carbonitrile

A mixture of 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 2 (239mg, 0.737mmol) and phosphorus oxychloride (339mg, 2.21mmol) in N,N-dimethylformamide (2mL) was stirred at room temperature for 1hr.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, saturated

sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and n-hexane to give the title compound (175mg, 77.5%) as pale yellow crystals.

MP : 110-112℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.86(3H, s), 6.94(4H, d, J=9Hz), 7.55(4H, d, J=9Hz).

IR (KBr) : 2240 cm^{-1}.

Example 4

N-Methoxy-4,5-bis(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide

To a solution of N,O-dimethylhydroxyamine hydrochloride (414mg, 4.24mmol) in tetrahydrofuran (8mL) was added triethylaluminum (15% solution in hexane) dropwise at 0℃ under nitrogen and the mixture was stirred at room temperature for 1hr. A solution of ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 1-2 (500mg, 1.41mmol) in tetrahydrofuran (10mL) was added dropwise to the mixture at 0℃ and the reaction mixture was stirred at 0℃ for 18hrs.

The mixture was poured into 1mol/L hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (475mg, 91.1%) as an amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.53(3H, br peak), 3.85(6H, s), 3.95(3H, s), 6.86-6.95(4H, m), 7.60(4H, s).

MS (ES+) : 369.53(M+H), 737.39(2M+H), 759.77(2M+Na).

Example 5

1-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]ethanone

To a solution of N-methoxy-4,5-bis(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 4 (120mg, 0.326mmol) in tetrahydrofuran (3mL) was added 1N solution of methylmagnesium bromide in tetrahydrofuran (1.0mL, 0.95mmol) dropwise at 0℃ under nitrogen and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and hexane to give the title compound (63mg, 59.8%) as pale yellow crystals.

MP : 139-140℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.72(3H, s), 3.85(3H, s), 3.86(3H, s), 6.90(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.63(2H, d, J=8Hz).

MS (ES+) : 324.40(M+H), 647.68(2M+H).

Example 6

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl](phenyl)methanone

The title compound (193mg, 61.5%) as yellow crystals was obtained from N-methoxy-4,5-bis(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 4 (300mg, 0.814mmol) and 3N solution of phenylmagnesium bromide in diethyl ether (0.82mL, 2.46mmol) in a manner similar to that of Example 5.

MP : 164-166℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 3.87(3H, s), 6.93(2H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.49-7.57(2H, m), 7.60-7.71(5H, m), 7.53-7.59(2H, m).

MS (ES+) : 386.30.

Example 7-1

2-(4-Methoxyphenyl)-3-(6-methoxy-3-pyridinyl)-3-oxopropanenitril e

To a stirred suspension of potassium tert-butoxide (3.69g, 32.9mmol) in tert-butanol (40mL) was added methyl 6-methoxynicotinate (5.0g, 29.9mmol) followed by dropwise addition of (4-methoxyphenyl)acetonitrile (4.4g, 29.9mmol) in tert-butanol (10mL) at room temperature. The resulting mixture was heated at 120℃ for 1.5hrs.

The mixture was allowed to cool and water was added to the mixture (160mL). The mixture was extracted with ether (100mL) and the aqueous phase was separated. The aqueous layer was neutralized with hydrogen chloride (37%) and then extracted with ethyl acetate (100mL). The organic layer was separated, washed with water (100mL) and brine (100mL), and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give the title compound (6.49g, 77%) as a brown viscous oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.80(3H, s), 3.99(3H, s), 5.44(1H, s), 6.78(1H, d, J=8.8Hz), 6.92(2H, d, J=8.8Hz), 7.35(2H, d, J=8.8Hz), 8.12(1H, dd, J=8.8,2.6Hz) , 8.78(1H, d, J=2.6Hz).

Example 7-2

1-(6-Hydroxy-3-pyridinyl)-2-(4-methoxyphenyl)ethanone

To a stirred solution of 2-(4-methoxyphenyl)-3-(6-methoxy-3-pyridinyl)-3-oxopropanenitril e obtained by Example 7-1 (4.19g, 14.8mmol) in 1,4-dioxane (20mL) was added hydrogen chloride (37%, 40mL), and the resulting mixture was heated at 80℃ for 20hrs.

The mixture was allowed to cool and the solvent was removed in vacuo. The residual solid was suspended in water (50mL) and the suspension was neutralized with saturated sodium bicarbonate solution. The precipitate was filtered and washed with water to

afford the title compound (3.17g, 88%) as a brown solid.

MP : 177-181℃.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.72(3H, s), 4.10(2H, s), 6.37(1H, d, J=9.6Hz), 6.87(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.87(1H, dd, J=9.6,2.6Hz) , 8.35(1H, d, J=2.6Hz).

Example 7-3

1-(6-Chloro-3-pyridinyl)-2-(4-methoxyphenyl)ethanone

A suspension of 1-(6-hydroxy-3-pyridinyl)-2-(4-methoxyphenyl)ethanone obtained by Example 7-2 (3.80g, 15.6mmol) in phosphorous oxychloride (12mL) was heated at 80℃ for 1hr.

The mixture was concentrated in vacuo and the residue was poured into ice-water (40mL). The mixture was neutralized with saturated sodium bicarbonate solution and stirred in ice bath for 1hr. The precipitate was filtered and washed with water to give the title compound (3.77g, 92%) as a pale brown solid.

MP : 77-81℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.79(3H, s), 4.21(2H, s), 6.87(2H, d, J=8.8Hz), 7.16(2H, d, J=8.8Hz), 7.42(1H, d, J=8.4Hz), 8.20(1H, dd, J=8.8,2.6Hz) , 8.98(1H, d, J=2.6Hz).

MS (ES+) : 262.00(M+1).

Example 7-4

2-(4-Methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone

To a stirred suspension of 1-(6-chloro-3-pyridinyl)-2-(4-methoxyphenyl)ethanone obtained by Example 7-3 (3.66g, 14mmol) in methanol (40mL) was added 5.19M solution of sodium methoxide in methanol (3.0mL, 15.4mmol) at room temperature and the resulting mixture was refluxed for 1.5hrs. Additional 5.19M solution of sodium methoxide in methanol (1.48mL,

7.7mmol) was added and the mixture was refluxed for 1.5hrs. The mixture was allowed to cool, methanol (10mL) was added to this mixture, and the mixture was neutralized with hydrogen chloride (37%). To the suspension was added water (10mL) and the mixture was stirred in ice bath for 1hr. The precipitate was filtered and washed with water (10mL) three times to afford the title compound (2.96g, 82%) as an off-white solid.

MP : 101-102°C.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.78(3H, s), 3.99(3H, s), 4.16(2H, s), 6.77(1H, d, J=8.8Hz), 6.86(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 8.16(1H, dd, J=8.8,2.6Hz) , 8.85(1H, d, J=2.6Hz).

MS (ES+) : 258.09(M+1).

Example 7-5

2-Azido-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone

To a solution of 2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 7-4 (3.0g, 11.7mmol) in dichloromethane (30mL) were added pyridinium tribromide (4.1g, 12.8mmol) and hydrogen bromide (33% solution in acetic acid, 3mL) at room temperature under nitrogen, and the mixture was stirred at the same temperature for 40min.

The reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in N,N-dimethylformamide (15mL). To the solution was added sodium azide (758mg, 11.7mmol) at 0°C and the mixture was stirred at room temperature for 1hr.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was

purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (1.5g, 43.1%) as an oil.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.77(3H, s), 3.92(3H, s), 5.55(1H, s), 6.70(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.20-7.40(3H, m), 8.06(1H, dd, J=8,2Hz) , 8.64(1H, d, J=2Hz).
MS (ES+) : 299.06.

Example 7-6
2-Amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone hydrochloride

A mixture of 2-azido-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 7-5 (1.5g, 5.03mmol), hydrochloric acid (37%, 0.42mL) and 10% palladium on carbon (300mg) in methanol (40mL) was stirred at room temperature under hydrogen for 30min.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was triturated with diethyl ether to give the title compound (1.46g, 94.0%) as a pale yellow powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.73(3H, s), 3.91(3H, s), 6.21-6.34(1H, m), 6.92(1H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 8.25(1H, dd, J=8,2Hz), 8.82-8.99(3H, m).

Example 7-7
2-Methoxy-N-[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxo ethyl]acetamide

To a solution of 2-amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 7-6 (150mg, 0.489mmol) and pyridine (115mg, 1.46mmol) in dichloromethane (3mL) was added methoxyacetyl chloride (74.6mg, 0.632mmol) under nitrogen at room temperature, and the mixture was stirred at the same temperature for 2hrs.

The mixture was pored into 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was washed with 1mol/L hydrochloric acid and water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (toluene : ethyl acetate=3:1) to give the title compound (100mg, 59.6%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.44(3H, s), 3.76(3H, s), 3.92(2H, s), 3.96(3H, s), 6.43(1H, d, J=8Hz), 6.74(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.31(2H, d, J=8Hz), 7.82(1H, d, J=8Hz), 8.12(1H, dd, J=8,2Hz), 8.80 (1H, d, J=2Hz).

Example 7-8

2-Methoxy-5-[2-(methoxymethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]pyridine

The title compound (32mg, 33.8%) was obtained as an amorphous from 2-methoxy-N-[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]acetamide obtained by Example 7-7 (100mg, 0.29mmol) in a manner similar to that of Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.52(3H, s), 3.84(3H, s), 3.97(3H, s), 4.60(2H, s), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.76(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).
MS (ES+) : 327.07.

Example 8-1

2-{[1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate

The title compound (673mg, 38%) was obtained from 2-amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 7-6 (1.47g, 4.76mmol) and acetoxyacetyl chloride (731mg, 6.19mmol) in a manner similar to that of Example 7-7.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.22(3H, s), 3.76(3H, s), 3.96(3H, s), 4.54(1H, d, J=15Hz), 4.62(1H, d, J=15Hz), 6.40(1H, d, J=8Hz), 6.74(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.31(2H, d, J=8Hz), 7.59(1H, d, J=8Hz), 8.11(1H, dd, J=8,2Hz), 8.80(1H, d, J=2Hz).
MS (ES+) : 373.06.

Example 8-2
[4-(4-Methoxyphenyl)-5-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol

To a solution of 2-{[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate obtained by Example 8-1 (670mg, 1.8mmol) in toluene (12mL) was added phosphorus oxychloride (828mg, 5.4mmol) at room temperature, and the mixture was heated to reflux with stirring for 15hrs.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in methanol. To a solution was added potassium carbonate (49.7mg) at room temperature and the mixture was stirred at the same temperature for 1hr.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) to give the title compound (26mg, 4.6%) as an amorphous solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.58(1H, t, J=7H), 3.84(3H, s), 3.97(3H, s), 4.81(2H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz),

7.53(2H, d, J=8Hz), 7.74(1H, dd, J=8,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 313.10.

Example 9-1

1-[4-(Benzyloxy)phenyl]-2-bromo-2-(4-methoxyphenyl)ethanone

The title compound (20.65g, 99.9%) was obtained as an oil from 1-[4-(benzyloxy)phenyl]- 2-(4-methoxyphenyl)ethanone (16.7g, 50.2mmol) in a manner similar to that of Example 78-3 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.80(3H, s), 5.12(2H, s), 6.36(1H, s), 6.89(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.31-7.50(7H, m), 7.96(2H, d, J=8Hz).

Example 9-2

2-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione

To a solution of 1-[4-(benzyloxy)phenyl]-2-bromo-2-(4-methoxyphenyl)ethanone obtained by Example 9-1 (20.65g, 50.2mmol) in N,N-dimethylformamide (200mL) was added potassium phthalimide (9.3g, 50.2mmol) at 0°C, and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with ethanol to give the title compound (20.47g, 85.4%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.77(3H, s), 5.07(2H, s), 6.70(1H, s), 6.85(2H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.30-7.47(7H, m), 7.65-7.73(2H, m), 7.78-7.88(4H, m).

Example 9-3

2-Amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride

To a suspension of 2-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione obtained by Example 9-2 (20.47g, 42.9mmol) in ethanol (200mL) was added hydrazine monohydrate (8.58g, 171mmol) at room temperature, and the mixture was heated to reflux with stirring for 30min.

After cooling, hydrochloric acid (37%, 24mL) was added to the mixture and the precipitate was filtered off. The filtrate was concentrated in vacuo and the residue was triturated with ethyl acetate to give the title compound (10.62g, 64.5%) as a powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.72(3H, s), 5.18(2H, s), 6.24(1H, br peak), 6.96(2H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.24-7.50(7H, m), 8.00(2H, d, J=8Hz), 8.77(2H, br peak).
MS (ES+) : 348.16.

Example 9-4
N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2-difluoroacetamide

To a mixture of difluoroacetic acid (981mg, 10.2mmol) and triethylamine (1.77g, 17.5mmol) in tetrahydrofuran (50mL) was added pivaloyl chloride (1.23g, 10.2mmol) dropwise at 0°C under nitrogen, and the mixture was stirred at the same temperature for 1hr. 2-Amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride obtained by Example 9-3 (2.8g, 7.29mmol) was added portionwise to the mixture at 0°C and the reaction mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of

solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=3:1) to give the title compound (2.0g, 64.5%) as an oil.

^{1}H NMR (300MHz, $CDCl_3$) : δ 3.76(3H, s), 5.09(2H, s), 5.89(1H, t, J=53Hz), 6.40(1H,br-s), 6.84(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.26-7.43(7H, m), 7.84-7.98(3H, m).

Example 9-5

5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole

To a mixture of triphenylphosphine (6.88g, 26.2mmol), iodine (6.66g, 26.2mmol) and triethylamine (5.31g, 52.5mmol) in dichloromethane (100mL) were added a solution of N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2-difluoroacetamide obtained by Example 9-4 (5.58g, 13.1mmol) in dichloromethane (10mL) at room temperature under nitrogen, and the mixture was stirred at the same temperature for 2days.

The reaction mixture was evaporated in vacuo, and partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=3:1) and triturated with petroleum ether to give the title compound (3.43g, 64.2%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 5.10(2H, s), 6.70(H, t, J=53Hz), 6.91(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.29-7.46(5H, m), 7.50-7.60(4H, m).

Example 10

4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (2.75g, 103.2%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 9-5 (3.42g, 8.39mmol) in a manner similar to that of Example 65 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 5.27(1H, s), 6.70(1H, t, J=53Hz), 6.85(2H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz)
MS (ES-) : 316.19.

Example 11
Ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate

To a suspension of sodium hydride (60% in oil, 410mg, 10.2mmol) in N,N-dimethylformamide (5mL) was added a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 10 (2.5g, 9.85mmol) in N,N-dimethylformamide (20mL) dropwise at 0℃ under nitrogen, and the mixture was stirred at the same temperature for 1hr. Then ethyl bromoacetate (1.64g, 9.85mmol) was added and stirred at the same temperature for 3hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystalized from a mixture of water and ethanol to give the title compound (2.66g, 83.7%) as crystals.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.31(3H, t, J=7.5Hz), 3.85(3H, s), 4.28(2H, q, J=7.5Hz), 4.66(2H, s), 6.69(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.54(2H, d, J=8Hz), 7.58(2H, d, J=8Hz)
MS (ES+) : 404.13.

Example 12

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

To a solution of ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate obtained by Example 11 (4.3g, 10.7mmol) in a mixture of diethyl ether (40mL) and tetrahydrofuran (10mL) was added lithium aluminum hydride (405mg, 10.7mmol) portionwise at 0℃ under nitrogen, and the mixture was stirred at the same temperature for 3hrs.

To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) and crystallized from a mixture of ethyl acetate and n-hexane to give the title compound (3.1g, 80.5%) as white crystals.

MP : 114-116℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.02(1H, t, J=7Hz), 3.85(3H, s), 3.98(2H, td, J=5,7Hz), 4.12(2H, t, J=5Hz), 6.70(1H, t, J=52Hz), 6.91(2H, d, J=8Hz),6.94(2H, d, J=8Hz), 7.52-7.60 (4H, m).

MS (ES+) : 362.13.

Example 13

3-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}-1-propanol

To a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 10 (40mg, 0.126mmol) in N,N-dimethylformamide

(1mL) were added 3-bromo-1-propanol (26.3mg, 0.189mmol) and potassium carbonate (52.3mg, 0.378mmol) at room temperature, and the mixture was stirred at the same temperature for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) to give the title compound (25mg, 52.8%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.64(1H, br peak), 2.01-2.14(2H, m), 3.84(3H, s), 3.88(2H, t, J=5Hz), 4.16(2H, t, J=5Hz), 6.69(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.50-7.60(4H, m).
MS (ES+) : 376.07.

Example 14
{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile

The title compound (241mg, 71.5%) was obtained as a powder from 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 10 (300mg, 0.946mmol) and iodoacetonitrile (316mg, 1.89mmol) in a manner similar to that of Example 13.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 4.82(2H, s), 6.71(1H, t, J=53Hz), 6.94(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.64(2H, d, J=8Hz).

Example 15
N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)acetamide

To a solution of {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]pheno

xy}acetonitrile obtained by Example 14 (97mg, 0.272mmol) in tetrahydrofuran (2mL) was added lithium aluminum hydride (12.4mg, 0.327mmol) at 0°C under nitrogen, and the mixture was stirred at the same temperature for 3hrs. To the reaction mixture was added water dropwise at 0°C.

The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in dichloromethane (2mL). To the solution were added pyridine (64.6mg, 0.817mmol) and acetyl chloride (25.6mg, , 0.327mmol) at 0°C, and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate : chloroform : n-hexane=12:7:1) to give the title compound (28mg, 25.6%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 2.03(3H, s), 3.68(2H, q, J=5Hz), 3.85(3H, s), 4.08(2H, t, J=5Hz), 5.93(1H, br peak), 6.70(1H, t, J=53Hz), 6.86-6.96(4H, m), 7.51-7.60(4H, m).
MS (ES+) : 403.10.

Example 16

tert-Butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

To a solution of {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile obtained by Example 14 (245mg, 0.688mmol) in tetrahydrofuran (2mL) was added lithium aluminum hydride (31.3mg,

0.825mmol) at 0℃ under nitrogen, and the mixture was stirred at the same temperature for 3hrs.

To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in dichloromethane (2mL). To a solution were added triethylamine (83.5mg, 0.115mmol) and di-tert-butyl dicarbonate (180mg, 0.115mmol) 0℃, and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate : n-hexane=1:1) to give the title compound (94mg, 29.7%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.56(2H, q, J=5Hz), 3.85(3H, s), 4.06(2H, t, J=5Hz), 4.99(1H, br peak), 6.70(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.51-7.59(4H, m).
MS (ES+) : 461.15.

Example 17

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine hydrochloride

4N Hydrogen chloride solution in ethyl acetate (0.5mL) was added to a solution of 1-tert-butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate obtained by Example 16 (92mg, 0.2mmol) in ethyl acetate (1mL) at room temperature. The mixture was stirred at the same temperature for 3hrs.

After evaporation of solvent, the residue was triturated with

ether to give the title compound (52mg, 65.6%) as an amorphous powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.24(2H, br pesk), 3.79(3H, s), 4.23(2H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.31(1H, t, J=53Hz), 7.50(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 8.09(3H, br peak).
MS (ES+) : 361.13.

Example 18
N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea

To a solution of 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine (136mg, 0.377mmol) in dichloromethane (3mL) was added trimethylsilyl isocyanate (87mg, 0.755mmol) at room temperature, and the mixture was stirred at the same temperature for 24hrs.

The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol=10:1) to give the title compound (95mg, 62.4%) as an amorphous powder.

MP : 146-149℃.
^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.25-3.40(2H, m), 3.80(3H, s), 4.00(2H, t, J=7Hz), 5.54(2H, s), 6.17(1H, t, J=7Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.29(1H, t, J=53Hz), 7.47-7.55(4H, m).

Example 19-1
Ethyl {[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate

The title compound (1.9g, 88.1%) was obtained as an oil from

2-amino-1-[4-(benzyloxy)phenyl]- 2-(4-methoxyphenyl)ethanone hydrochloride (1.85g, 4.82mmol) and ethyl chlorooxoacetate (888mg, 6.51mmol) in a manner similar to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.37(3H, t, J=7.5Hz), 3.75(3H, s), 4.34(2H, q, J=7.5Hz), 5.08(2H, s), 6.42(1H, d, J=7.5Hz), 6.82(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.29-7.45(7H, m), 7.94(2H, d, J=8Hz), 8.48(1H, d, J=7.5Hz).
MS (ES+) : 448.14.

Example 19-2
Ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate

The title compound (1.06g, 58.3%) was obtained as an oil from ethyl {[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 19-1 (1.9g, 4.25mmol) in a manner similar to that of Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.45(3H, t, J=7.5Hz), 3.84(3H, s), 4.50(2H, q, J=7.5Hz), 5.10(2H, s), 6.91(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.30-7.46(5H, m), 7.55-7.65(4H, m).
MS (ES+) : 430.14.

Example 20
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (980mg, 99.2%) was obtained as a powder from ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 19-2 (1.06g, 2.47mmol) in a manner similar to that of Example 2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.09(2H, s), 5.76(1H, br peak),

6.90-7.04(5H, m), 7.30-7.46(5H, m), 7.56(2H, d, J=8Hz), 7.61(2H, d, J=8Hz).
MS (ES+) : 401.12.

Example 21
5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (298mg, 91.6%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 20 (420mg, 1.05mmol) in a manner similar to that of Example 65 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.80(3H, s), 6.84(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.43(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.90(1H, s), 8.26(1H, s), 9.98(1H, s).
MS (ES-) : 309.20.

Example 22
5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (200mg, 58.8%) was obtained as a powder from 5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 21 (298mg, 0.96mmol) and chloroethanol (193mg, 2.4mmol) in a manner similar to that of Example 87 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.01(1H, t, J=7Hz), 3.85(3H, s), 4.03(2H, dd, J=7,5Hz), 4.12(2H, t, J=5Hz), 5.14(1H, br-s), 6.87-6.95(4H, m), 6.98(1H, br peak), 7.55(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES+) : 355.20.

Example 23

5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbonitrile

To a solution of 5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 22 (55.4mg, 0.156mmol) and pyridine (61.8mg, 0.782mmol) in dichloromethane (2mL) was added trifluoroacetic anhydride (75.5mg, 0.36mmol) under nitrogen at room temperature, and the mixture was stirred at the same temperature for 1hr.

The mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid and water, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in methanol (5mL) and the solution was allowed to stand at room temperature for 18hrs.

After evaporation of solvent, the residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1), and triturated with a mixture of petroleum ether and diethyl ether to give the title compound (26 mg, 49.4%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.00(1H, t, J=7Hz), 3.85(3H, s), 4.00(2H, dd, J=7,5Hz), 4.14(2H, t, J=5Hz), 6.93(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.51-7.60(4H, m).

MS (ES+) : 337.15.

Example 24

2-{4-[2-(Aminocarbonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate

The title compound (102mg, 85.2%) was obtained as an oil from 5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 22 (107mg, 0.302mmol) in a manner similar to that of Example 39-1 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.11(3H, s), 3.85(3H, s), 4.20(2H, t, J=5Hz), 4.44(2H, t, J=5Hz), 5.66(1H, br s), 6.91(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.99(1H, br s), 7.55(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES+) : 397.12.

Example 25
2-{4-[2-Cyano-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate

The title compound (80mg, 83.8%) was obtained as an oil from 2-{4-[2-(aminocarbonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate obtained by Example 24 (100mg, 0.252mmol) in a manner similar to that of Example 3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.11(3H, s), 3.85(3H, s), 4.23(2H, t, J=5Hz), 4.45(2H, t, J=5Hz), 6.89-6.99(4H, m), 7.50-7.60(4H, m).

Example 26
5-[4-(Cyanomethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (383mg, 86.6%) was obtained as an oil from 5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 21 (393mg, 1.27mmol) and iodoacetonitrile (423mg, 2.53mmol) in a manner similar to that of Example 13.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 4.81(2H, s), 5.65(1H, br-s), 6.91-7.04(5H, m), 7.55(2H, d, J=8Hz), 7.68(2H, d, J=8Hz).
MS (ES+) : 350.11.

Example 27

5-[4-(2-Aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

To a mixture of 5-[4-(cyanomethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 26 (150mg, 0.429mmol) and cobalt(II) chloride hexahydrate (30.6mg, 0.129mmol) in methanol (3mL) was added sodium borohydride (162mg, 4.29mmol) portionwise in water bath under nitrogen, and the mixture was stirred in water bath for 15min. 1N Sodium hydroxide solution (0.5mL) was added to the mixture and the reaction mixture was stirred for 30min.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was partitioned between water and chloroform. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol=10:1) to give the title compound (77mg, 50.7%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.85(3H, s), 4.02(2H, t, J=5Hz), 5.61 (1H, br-s), 6.90(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.99(1H, br-s), 7.56(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).

Example 28

5-{4-[2-(Acetylamino)ethoxy]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (47mg, 60%) was obtained as an oil from 5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 27 (70mg, 0.198mmol) in a manner similar to that of Example 39-1 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.03(3H, s), 3.70(2H, q, J=5Hz), 3.85(3H, s), 4.07(2H, t, J=5Hz), 5.96(1H, br-s), 6.10(1H, br-s), 6.89(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.11(1H, br-s), 7.54(2H, d, J=8Hz),

7.60(2H, d, J=8Hz).
MS (ES+) : 396.13.

Example 29
N-(2-{4-[2-Cyano-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)acetamide

The title compound (26mg, 56.2%) was obtained as a powder from 5-{4-[2-(acetylamino)ethoxy]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 28 (48.5mg, 0.123mmol) in a manner similar to that of Example 23.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.05(3H, s), 3.69(2H, q, J=5Hz), 3.85(3H, s), 4.09(2H, t, J=5Hz), 5.91(1H, br peak), 6.88-6.96(4H, m), 7.50-7.60(4H, m).
MS (ES+) : 378.10.

Example 30-1
(2E)- and (2Z)-2-[4-(Benzyloxy)phenyl]-3-(6-methoxy-3-pyridinyl)-2-propenoic acid

The title compound was obtained in a manner similar to that of Example 91-3 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.81(15/8H, s), 3.87(9/8H, s), 5.13(10/8H, s), 5.15(6/8H, s), 6.64(5/8H, d, J=8Hz), 6.86(3/8H, d, J=8Hz), 6.93(3/8H, s), 7.03-7.12(2H, m), 7.18(5/8H, dd, J=8,2Hz), 7.32-7.50(7H, m), 7.70(5/8H, s), 7.80(3/8H, dd, J=8,2Hz), 8.04(5/8H, d, J=2Hz), 8.28(3/8H, d, J=2Hz).

Example 30-2
1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone

The title compound was obtained from (2E)- and (2Z)-2-[4-(benzyloxy)phenyl]-3-(6-methoxy-3-pyridinyl)-2-propeno

ic acid obtained by Example 30-1 in a manner similar to that of Example 91-4 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.92(3H, s), 4.16(2H, s), 5.14(2H, s), 6.72(1H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.45(5H, m), 7.49(1H, dd, J=8,2Hz), 7.99(2H, d, J=8Hz), 8.02(1H, d, J=2Hz).
MS (ES+) : 334.15.

Example 30-3
1-[4-(Benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)ethanone

The title compound (21.2g, 78.1%) was obtained as a powder from 1-[4-(benzyloxy)phenyl]-2-(6- methoxy-3-pyridinyl)ethanone obtained by Example 30-2 (22g, 66mmol) and pyridinium tribromide (23.2g, 72.6mmol) in a manner similar to that of Example 68-1 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.95(3H, s), 5.14(2H, s), 6.26(1H, s), 6.80(1H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.46(5H, m), 7.92(1H, dd, J=8,2Hz), 8.01(2H, d, J=8Hz), 8.21(1H, d, J=2Hz).
MS (ES+) : 411.98, 413.95.

Example 30-4
2-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione

The title compound (20.0g, 81.2%) was obtained as a powder from 1-[4-(benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)ethanone obtained by Example 30-3 (21.2g, 51.5mmol) and potassium phthalimide (9.54g, 51.3mmol) in a manner similar to that of Example 9-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.91(3H, s), 5.07(2H, s), 6.65-6.72(2H, m), 6.93(2H, d, J=8Hz), 7.27-7.41(5H, m), 7.66-7.78(3H, m),

7.78-7.88(4H, m), 8.26(1H, d, J=2Hz).

Example 30-5

2-Amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride

The title compound (2.67g, 110%) was obtained from 2-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione obtained by Example 30-4 (3.0g, 6.27mmol) in a manner similar to that of Example 9-3.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.82(3H, s), 5.18(2H, s), 6.32(1H, br peak), 6.85(1H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.26-7.50(5H, m), 7.71(1H, dd, J=8,2Hz), 8.02(2H, d, J=8Hz), 8.40(1H, d, J=2Hz), 8.91(2H, br peak).

Example 30-6

N-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2-difluoroacetamide

To a solution of difluoroacetic acid (799mg, 8.33mmol) in tetrahydrofuran (8mL) were added oxalyl chloride (1.06g, 8.33mmol) and N,N-dimethylformamide (1drop) at 0℃ under nitrogen, and the mixture was stirred at room temperature for 1hr. The mixture was added to a mixture of 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 30-5 (2.67g, 6.94mmol) and triethylamine (2.11g, 20.8mmol) in dichloromethane (25mL) at 0℃, and the reaction mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=3:1) to give the title compound (1.25g,

42.6%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.89(3H, s), 5.10(2H, s), 5.89(1H, t, J=53Hz), 6.40(1H, d, J=8Hz), 6.68(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.31-7.42(5H, m), 7.53(1H, dd, J=8,2Hz), 7.89-8.00(3H, m), 8.25(1H, d, J=2Hz).

Example 30-7

5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound (840mg, 70.2%) was obtained as a powder from N-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2-difluoroacetamide obtained by Example 30-6 (1.25g, 2.93mmol) in a manner similar to that of Example 9-5.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 5.10(2H, s), 6.70(1H, t, J=53Hz), 6.77(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.30-7.48(5H, m), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

Example 31

4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 30-7 (830mg, 2.03mmol) and dry 20% palladium hydroxide on carbon (240mg) in ethanol (8mL) and cyclohexene (4mL) was stirred at reflux condition for 2hrs, and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give the title compound (630mg, 97.8%) as a powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.89(3H, s), 6.86(2H, d, J=9Hz), 6.91(1H, d, J=9Hz), 7.30(1H, t, J=53Hz), 7.84(1H, dd, J=9,2Hz), 8.36(1H, d,

J=2Hz).

Example 32

Ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate

The title compound (830mg, 105%) was obtained as a powder from 4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol obtained by Example 31 (620mg, 1.95mmol) and ethyl bromoacetate (390mg, 2.34 mmol) in a manner similar to that of Example 11.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.32(3H, t, J=7Hz), 3.97(3H, s), 4.28(2H, q, J=7Hz), 4.66(2H, s), 6.69(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.80(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 405.11.

Example 33

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (630mg, 82.2%) was obtained as crystals from ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate (855mg, 2.11mmol) obtained by Example 32 in a manner similar to that of Example 12.

MP : 126-128℃.
^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.01(1H, t, J=6Hz), 3.98(3H, s), 4.00(2H, dd, J=6,5Hz), 4.13(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.77(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).
MS (ES+) : 363.14.

Example 34

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 33 (203mg, 0.56mmol) and triethylamine (85mg, 0.84mmol) in dichloromethane (4mL) was added methanesulfonyl chloride (86.3mg, 0.84mmol) at 0°C under nitrogen, and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and chloroform. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (247mg, 100.1%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.11(3H, s), 3.97(3H, s), 4.29(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).

Example 35

2-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 34 (247mg, 0.561mmol) in N,N-dimethylformamide (5mL) was added potassium phthalimide (156mg, 0.841mmol) at room temperature, and the mixture was stirred at 60°C for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried

over magnesium sulfate, and evaporated in vacuo to give the title compound (260mg, 94.3%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.96(3H, s), 4.13 (1H, t, J=7Hz), 4.27(1H, t, J=7Hz), 6.69(1H, t, J=53Hz), 6.76(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.79(2H, d, J=8Hz), 7.70-7.81(3H, m), 7.84-7.91(2H, m), 8.39(1H, d, J=2Hz).

Example 36

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

To a solution of 2-(2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 35 (260mg, 0.529mmol) in acetonitrile (5mL) was added hydrazine monohydrate (212mg, 4.23mmol) at room temperature, and the mixture was stirred at 60℃ for 5hrs.

After cooling, the precipitate was filtered off. The filtrate was concentrated in vacuo to give the title compound (184mg, 96.2%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.97(3H, s), 4.03(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).
MS (ES+) : 362.13.

Example 37

N-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (46mg, 47.8%) was obtained as a powder from 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 36 (86mg, 0.238mmol) in a manner similar to that of Example

18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.28-3.40(2H, m), 3.89(3H, s), 4.00(2H, t, J=5Hz), 5.55(2H, s), 6.18(1H, t, J=5Hz), 6.92(1H, d, J=9Hz), 7.09(2H, d, J=9Hz), 7.33(1H, t, J=53Hz), 7.52(2H, d, J=9Hz), 7.83(1H, dd, J=9,2Hz), 8.37(1H, d, J=2Hz).
MS (ES+) : 405.13.

Example 38
N-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 36 (80mg, 0.221mmol) and triethylamine (27mg, 0.266mmol) in dichloromethane (2mL) was added methanesulfonyl chloride (30.4mg, 0.266mmol) at 0°C under nitrogen, and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (52mg, 53.4%) as an oil.

H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.58(2H, q, J=7Hz), 3.97(3H, s), 4.15(2H, t, J=7Hz), 4.76(1H, t, J=7Hz), 6.70(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).
MS (ES+) : 440.11.

Example 39-1
N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide

To a suspension of 2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride (1.56g, 4.14mmol) in dichloromethane (16mL) were added triethylamine (503mg, 4.97mmol) and trifluoroacetic anhydride (1.04g, 4.97mmol) at 0°C under nitrogen, and the mixture was stirred at room temperature for 2hrs.

The reaction mixture was evaporated in vacuo, and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was triturated with hexane to give the title compound (1.20g, 65.3%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.76(3H, s), 5.09(2H, s), 6.35(1H, d, J=7Hz), 6.84(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.26-7.44(7H, m), 7.87-8.00(3H, m).
MS (ES-) : 442.26.

Example 39-2
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazole

The title compound (860mg, 74.7%) was obtained as a powder from N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide obtained by Example 39-1 (1.2g, 2.71mmol) in a manner similar to that of Example 9-5.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.11(2H, s), 6.80(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.26-7.46(5H, m), 7.51-7.60(4H, m).

Example 40
4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol

The title compound (655mg, 96.6%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazole obtained by Example 39-2 (60mg, 2.02 mmol) in a manner similar to that of Example 65 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.79(3H, s), 6.85(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.42(2H, d, J=8Hz), 7.52(2H, d, J=8Hz).
MS (ES-) : 334.20.

Example 41
2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (742mg, 98.6%) was obtained as a powder from 4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol obtained by Example 40 (665mg, 1.95mmol) and 2-chloroethanol (958mg, 11.9mmol) in a manner similar to that of Example 87 described later.

MP : 98-100℃.
^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.00(1H, t, J=7Hz), 3.85(3H, s), 4.00(2H, dt, J=7,5Hz), 4.13(1H, t, J=5Hz), 6.91(2H, d, J=8Hz), 7.05(2H, d, J=8Hz), 7.51-7.61(4H, m).

Example 42
2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (895mg, 100%) was obtained as an oil from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 41 (742mg, 1.96mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.12(3H, s), 3.87(3H, s), 4.30(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.87-6.99(4H, m), 7.53-7.63(4H, m).

Example 43

2-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (1.03g, 103%) was obtained as a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 42 (895mg, 1.96mmol) and potassium phthalimide (544mg, 2.93mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 4.11(2H, t, J=5Hz), 4.26(2H, t, J=5Hz), 6.83-6.95(4H, m), 7.45-7.58(4H, m), 7.68-7.80(2H, m), 7.80-7.93(2H, m).

Example 44

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanamine

2-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 43 (1.03g, 2.03mmol) was dissolved in a solution of 40% methylamine in methanol (5mL) at room temperature and the mixture was stirred at the same temperature for 1day.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and diethyl ether. The water layer was adjusted to pH10 with saturated sodium bicarbonate solution and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (chloroform : methanol=40:1) to give the title compound (575mg, 75%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.09-3.20(2H, m), 3.85(3H, s), 4.05(2H, t, J=5Hz), 6.90(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).
MS (ES+) : 379.12.

Example 45
N-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (58mg, 52.1%) was obtained as a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 44 (100mg, 0.264mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.25-3.40(2H, m), 3.79(3H, s), 4.00(2H, t, J=5Hz), 5.55(2H, s), 6.19(1H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.55(2H, d, J=8Hz).

Example 46
N-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (64.9mg, 53.8%) was obtained as a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 44 (100mg, 0.264mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.03(3H, s), 3.53-3.61(2H, m), 3.84(3H, s), 4.15(2H, t, J=5Hz), 4.70-4.80(1H, m), 6.85-6.95(4H, m), 7.51-7.61(4H, m).
MS (ES-) : 455.18.

Example 47

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine hydrochloride

To a solution of 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 44 (288mg, 0.761mmol) in methanol (5mL) was added 10% hydrogen chloride in methanol (1mL) at room temperature. The reaction mixture was stirred at the same temperature for 30min.

The solution was evaporated in vacuo and the residue was washed with diethyl ether to give the title compound (302mg, 95.6%) as a yellow amorphous powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.18-3.30(2H, m), 3.80(3H, s), 4.24(2H, t, J=5Hz), 7.01(2H, d, J=8Hz), 7.11(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.58 (2H, d, J=8Hz), 8.14(3H, br peak).

Example 48-1

N-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2,2-trifluoroacetamide

The title compound (824mg, 42%) was obtained as a powder from 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 30-5 (1.7g, 4.42mmol) and trifluoroacetic anhydride (1.21g, 5.74mmol) in a manner similar to that of Example 39-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.89(3H, s), 5.10(2H, s), 6.31-6.48(1H, m), 6.68(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.26-7.45(5H, m), 7.53(1H, dd, J=8,2Hz), 7.91(2H, d, J=8Hz), 8.26(1H, d, J=2Hz).

Example 48-2

5-[5-[4-(Benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound (607mg, 79.1%) was obtained as a powder from N-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2,2-trifluoroacetamide obtained by Example 48-1 (800mg, 1.8mmol) in a manner similar to that of Example 9-5.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 5.11(2H, s), 6.78(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.30-7.49(5H, m), 7.54(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 427.12.

Example 49

4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol

The title compound (423mg, 88.4%) was obtained as a powder from 5-[5-[4-(benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 48-2 (607mg, 1.42mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 6.81(1H, d, J=8Hz), 6.88(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 7.89(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).
MS (ES-) : 335.12.

Example 50

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (305mg, 65.8%) was obtained as a powder from 4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol obtained by Example 49 (410mg, 1.22mmol) and 2-chloroethanol (584mg, 7.32mmol) in a manner

similar to that of Example 87 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.99(1H, t, J=7Hz), 3.97(3H, s), 3.99(2H, dt, J=7,5Hz), 4.12(1H, t, J=5Hz), 6.79(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 381.08.

Example 51

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (355mg, 99.8%) was obtained as an oil from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 50 (295mg, 0.776mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.11(3H, s), 3.97(3H, s), 4.29(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.80(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).
MS (ES+) : 459.03.

Example 52

2-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (395mg, 100%) was obtained as a powder from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 51 (355mg, 0.774mmol) and potassium phthalimide (125mg, 1.16mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 4.14(2H, t, J=5Hz), 4.28(2H,

t, J=5Hz), 6.77(1H, d, J=9Hz), 6.92(2H, d, J=9Hz), 7.50(2H, d, J=9Hz), 7.69-7.91(5H, m), 8.39(1H, d, J=2Hz).

Example 53

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (153mg, 53.4%) was obtained as an oil from 2-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 52 (385mg, 0.756mmol) in a manner similar to that of Example 36.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.97(3H, s), 4.03(2H, t, J=5Hz), 6.79(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

Example 54

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (53mg, 61.3%) was obtained as an oil from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 53 (71.7mg, 0.189mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.59(2H, dd, J=6,5Hz), 3.97(3H, s), 4.15(2H, t, J=5Hz), 4.75(1H, t, J=6Hz), 6.80(1H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 55

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (52mg, 59.6%) was obtained as a powder from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 53 (79.3mg, 0.201mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, $CDCl_3$: CD_3OD=10:1) : δ 3.58(2H, t, J=5Hz), 3.97(3H, s), 4.07(2H, t, J=5Hz), 6.81(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.85(1H, dd, J=8,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 423.15.

Example 56-1
N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2-methylpropanamide

The title compound (688mg, 63.3%) was obtained as a powder from 2-amino-1-[4-(benzyloxy)phenyl]- 2-(4-methoxyphenyl)ethanone hydrochloride obtained by Example 9-3 (1.0g, 2.61mmol) and isobutyryl chloride (333mg, 3.13mmol) in a manner similar to that of Example 7-7.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3H, d, J=7.5Hz), 1.16(3H, d, J=7.5Hz), 2.34-2.51(1H, m), 3.75(3H, s), 5.08(2H, s), 6.44(1H, d, J=7Hz), 6.81(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.98(1H, d, J=7Hz), 7.26-7.41(7H, m), 7.94(2H, d, J=8Hz).
MS (ES+) : 418.16.

Example 56-2
5-[4-(Benzyloxy)phenyl]-2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazole

The title compound (422mg, 74.7%) was obtained as an oil from N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2-methylpropanamide obtained by Example

56-1 (590mg, 1.41mmol) in a manner similar to that of Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.24(1H, m), 3.83(3H, s), 5.09(2H, s), 6.89(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.29-7.45(5H, m), 7.45(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 400.25.

Example 57
4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (222mg, 67.9%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 56-2 (422mg, 1.06mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.08-3.24(1H, m), 3.83(3H, s), 6.81(2H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).
MS (ES+) : 310.24.

Example 58
2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (163mg, 66.4%) was obtained as a powder from 4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 57 (215mg, 0.695mmol) and 2-chloroethanol (336mg, 4.17mmol) in a manner similar to that of Example 87 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 2.05(1H, t, J=6Hz), 3.04-3.25(1H, m), 3.83(3H, s), 3.94-4.01(2H, m), 4.10(2H, t, J=5Hz), 6.85-6.94(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

Example 59
2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}et

hyl methanesulfonate

The title compound (132mg, 101%) was obtained as an oil from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 58 (107mg, 0.303mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.10(3H, s), 3.11-3.25(1H, m), 3.83(3H, s), 4.24-4.30(2H, m), 4.55-4.61(2H, m), 6.84-6.92(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 432.15.

Example 60

2-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (150mg, 103%) was obtained as an oil from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 59 (130mg, 0.301mmol) and potassium phthalimide (83.7mg, 0.452mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.40(6H, d, J=7Hz), 3.06-3.18(1H, m), 3.81(3H, s), 4.11(2H, t, J=5Hz), 4.24(2H, t, J=5Hz), 6.80-6.91(4H, m), 7.45(2H, d, J=9Hz), 7.52(2H, d, J=9Hz), 7.70-7.79(2H, m), 7.83-7.90(2H, m).

Example 61

2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (106mg, 96.8%) was obtained as an oil from 2-(2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 60 (150mg, 0.311mmol) in a manner similar to that

of Example 36.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.21(1H, m), 3.83(3H, s), 4.00(2H, t, J=5Hz), 6.81-6.93(4H, m), 7.47(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

Example 62

N-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (23mg, 43.8%) was obtained as a powder from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 61 (43mg, 0.122mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.04(3H, s), 3.08-3.22(1H, m), 3.56(2H, q, J=5Hz), 3.83(3H, s), 4.12(2H, t, J=5Hz), 4.75(1H, br peak), 6.85(2H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.50(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

MS (ES+) : 431.13.

Example 63

N-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (23mg, 32.5%) was obtained as an oil from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 62 (63mg, 0.179mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.08-3.21(1H, m), 3.61(2H, q, J=5Hz), 3.83(3H, s), 4.05(2H, t, J=5Hz), 4.40(2H, br-s), 4.95(1H, br peak), 6.85(2H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

MS (ES+) : 396.20.

Example 64-1

1,2-Bis(4-methoxyphenyl)-2-oxoethyl (benzyloxy)acetate

To a solution of anisoin (500mg, 1.84mmol) and pyridine (581mg, 7.34mmol) in dichloromethane (10mL) was added benzyloxyacetyl chloride (424mg, 2.30mmol) under nitrogen at room temperature, and the mixture was stirred at the same temperature for 22hrs.

The mixture was poured into 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was washed with 1mol/L hydrochloric acid and water, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (775 mg, 100.4%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.78(3H, s), 3.83(3H, s), 4.21(1H, d, J=17Hz), 4.32(1H, d, J=17Hz), 4.68(2H, s), 6.82-6.92(5H, m), 7.21-7.42(7H, m), 7.91(2H, d, J=8Hz).

Example 64-2

2-[(Benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole

To a solution of 1,2-bis(4-methoxyphenyl)-2-oxoethyl (benzyloxy)acetate obtained by Example 64-1 (775mg, 1.84mmol) in acetic acid (14mL) was added ammonium acetate (1.42g, 18.4mmol) at room temperature, and the mixture was heated to reflux with stirring for 1hr.

After cooling, the reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) and triturated with ethanol to give the title compound (300mg, 40.5%) as a pale yellow powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.84(6H, s), 4.67(2H, s), 4.70(2H, s), 6.84-6.94(4H, m), 7.26-7.44(5H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

MS (ES+) : 402.12.

Example 65

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

A mixture of 2-[(benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole obtained by Example 64-2 (88mg, 0.219mmol) and 10% palladium on carbon (20mg) in a mixture of methanol (2mL) and tetrahydrofuran (2mL) was stirred at room temperature under hydrogen for 6hrs.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1), and triturated with a mixture of hexane and diethyl ether to give the title compound (44mg, 65.4%) as a pale yellow powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.36(1H, t, J=7Hz), 3.84(6H, s), 4.79(2H, d, J=7Hz), 6.85-6.94(4H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

MS (ES+) : 312.13.

Example 66-1

1,2-Bis(4-methoxyphenyl)-2-oxoethyl ethyl malonate

The title compound (644mg, 90.8%) was obtained as an oil from anisoin (500mg, 1.84mmol) and ethyl 3-chloro-3-oxopropionate (346mg, 2.30mmol) in a manner similar to that of Example 64-1.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.26(3H, t, J=7.5Hz), 3.53(2H, s), 3.79(3H, s), 3.83(3H, s), 4.20(2H, q, J=7.5Hz), 6.81-6.93(5H, m), 7.38(2H, d, J=8Hz), 7.91(2H, d, J=8Hz).

Example 66-2

Ethyl [4,5-bis(4-methoxyphenyl)-1,3-oxazol-2- yl]acetate

The title compound (186mg, 30.4%) was obtained an oil from 1,2-bis(4-methoxyphenyl)-2-oxoethyl ethyl malonate obtained by Example 66-1 (644mg, 1.67mmol) and ammonium acetate (1.28g, 16.7mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.31(3H, t, J=7.5Hz), 3.84(6H, s), 3.92(2H, s), 4.25(2H, q, J=7.5Hz), 6.90(4H, d, J=8Hz), 7.45-7.65(4H, m).
MS (ES+) : 368.14.

Example 67

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]acetic acid

To a solution of ethyl [4,5-bis(4-methoxyphenyl)-1,3-oxazol-2-yl]acetate obtained by Example 66-2 (70mg, 0.191mmol) in ethanol (2mL) was added 1 mol/L sodium hydroxide solution (0.25mL) at room temperature, and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was evaporated in vacuo and dissolved in water. The water solution was washed with ether, adjusted to pH1 with 6N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diethyl ether to give the title compound (31mg, 47.9%) as an amorphous powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.63(2H, br-s), 3.77(3H, s), 3.79(3H, s), 6.95(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.43(2H, d, J=8Hz), 7.49(2H, d, J=8Hz).
MS (ES+) : 340.15.

Example 68-1

2-Bromo-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone

To a solution of 2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone (1.0g, 3.89mmol) in dichloromethane (10mL) were added pyridinium tribromide (1.37g, 4.28mmol) and hydrogen bromide (33% solution in acetic acid, 1mL) at room temperature under nitrogen, and the mixture was stirred at the same temperature for 40min.

The reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (1.32g, 101%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.80(3H, s), 3.99(3H, s), 6.29(1H, s), 6.77(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.45(2H, d, J=8Hz), 8.16(1H, dd, J=8,2Hz), 8.80(1H, d, J=2 Hz).

Example 68-2

2-Hydroxy-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone

2-Bromo-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 68-1 (1.30g, 3.87mmol) was dissolved in acetone (10mL) and water (5mL), and heated to reflux for 1hr.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (770mg, 72.9%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.77(3H, s), 3.96(3H, s), 4.46(1H, d, J=7Hz), 5.80(1H, d, J=7Hz), 6.74(1H, d, J=8Hz), 6.86(2H, d, J=8Hz), 7.25(2H, d, J=8Hz), 8.10(1H, dd, J=8,2Hz), 8.72(1H, d, J=2Hz).

Example 68-3

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl methoxyacetate

The title compound (128mg, 101.3%) was obtained as an oil from 2-hydroxy-2-(4-methoxyphenyl)-1-(6- methoxy-3-pyridinyl)ethanone obtained by Example 68-2 (100mg, 0.366mmol) and methoxyacetyl chloride (47.7mg, 0.439mmol) in a manner similar to that of Example 64-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.88(3H, s), 3.96(3H, s), 4.16(1H, d, J=17Hz), 4.25(1H, d, J=17Hz), 6.74(1H, d, J=8Hz), 6.80(1H, s), 6.90(2H, d, J=8Hz), 7.36(2H, d, J=8Hz), 8.10(1H, dd, J=8,2Hz), 8.75(1H, d, J=2Hz).

Example 68-4

2-Methoxy-5-[2-(methoxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]pyridine

The title compound (80mg, 66.1%) was obtained as an oil from 1-(4-methoxyphenyl)-2-(6-methoxy-3- pyridinyl)-2-oxoethyl methoxyacetate obtained by Example 68-3 (128mg, 0.371mmol) and ammonium acetate (286mg, 3.71mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.52(3H, s), 3.84(3H, s), 3.96(3H, s), 4.60(2H, s), 6.75(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 69-1

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl (acetyloxy)acetate

The title compound (990mg, 100.2%) was obtained as an oil from 2-hydroxy-2-(4-methoxyphenyl)-1-(6- methoxy-3-pyridinyl)ethanone

obtained by Example 68-2 (725mg, 2.65mmol) and acetoxyacetyl chloride (542mg, 3.97mmol) in a manner similar to that of Example 64-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.15(3H, s), 3.79(3H, s), 3.96(3H, s), 4.74(1H, d, J=17Hz), 4.81(1H, d, J=17Hz), 6.74(1H, d, J=8Hz), 6.77(1H, s), 6.90(2H, d, J=8Hz), 7.37(2H, d, J=8Hz), 8.09(1H, dd, J=8,2Hz), 8.74(1H, d, J=2Hz).

Example 69-2

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate

The title compound (415mg, 48%) was obtained as an oil from 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 69-1 (990mg, 2.65mmol) and ammonium acetate (2.04g, 26.5mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.18(3H, s), 3.84(3H, s), 3.96(3H, s), 5.22(2H, s), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 70

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol

To a solution of [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate obtained by Example 69-2 (410mg, 1.26mmol) in methanol (8mL) was added potassium carbonate (208mg, 1.51mmol) at room temperature, and the mixture was stirred at the same temperature for 1hr.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated

sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) and triturated with isopropyl ether to give the title compound (247mg, 63.0%) as an amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.61(1H, t, J=7Hz), 3.84(3H, s), 3.97(3H, s), 4.80(2H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 313.06.

Example 71
5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carb aldehyde

A mixture of [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol obtained by Example 70 (192mg, 0.615mmol) and manganese(IV) oxide (187mg, 2.15mmol) in chloroform (5mL) was heated to reflux with stirring for 2hrs.
After cooling, the reaction mixture was filtered through Celite and evaporated in vacuo. The residue was triturated with petroleum ether to give the title compound (178mg, 93.3%) as an amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 3.99(3H, s), 6.81(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 8.48(2H, d, J=8Hz), 9.78(1H, s).

Example 72
[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanol

To a solution of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carb aldehyde obtained by Example 71 (70mg, 0.226mmol) in tetrahydrofuran

(3mL) was added 3N solution of phenylmagnesium bromide in diethyl ether (0.1mL, 0.3mmol) dropwise at 0℃ under nitrogen, and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (62.3mg, 71.1%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.30(1H, d, J=7Hz), 3.82(3H, s), 3.96(3H, s), 5.93(1H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.32-7.46(5H, m), 7.55(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).
MS (ES+) : 389.10.

Example 73
[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanone

The title compound (42mg, 70.4%) was obtained as yellow crystals from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanol obtained by Example 72 (60mg, 0.154mmol) in a manner similar to that of Example 71.

MP : 156-158℃.
^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.87(3H, s), 3.99(3H, s), 6.82(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.50-7.58(2H, m), 7.62-7.70(3H, m), 7.90(1H, dd, J=8,2Hz), 8.53-8.59(3H, m).
MS (ES+) : 387.05.

Example 74
5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylic acid

To a suspension of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carb aldehyde obtained by Example 71 (103mg, 0.332mmol) in a mixture of water (0.8mL) and tert-buthylalcohol (3mL) were added 2-methyl-2-butene (103mg, 1.47mmol) and sodium dihydrogenphosphate (43.8mg, 0.365mmol) in water bath. To the mixture was added sodium chlorite (133mg, 1.47mmol) portionwise and the resulting mixture was stirred in water bath for 1.5hrs.

The reaction mixture was evaporated in vacuo, and the residue was dissolved in water. The solution was adjusted to pH4 with 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound (110mg, 101.6%) as an amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.97(3H, s), 6.80(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.87(2H, d, J=8Hz), 8.44(1H, s).
MS (ES+) : 327.03.

Example 75
5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carb oxamide

A mixture of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carb oxylic acid obtained by Example 74 (110mg, 0.337mmol), 1-hydroxybenzotriazole (61.5mg, 0.455mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84mg, 0.438mmol) in N,N-dimethylformamide (6mL) was added ammonia solution (28%, 27mg, 0.438mmol) at 0°C, and the mixture was stirred at the same temperature for 18hrs.

The mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over

magnesium sulfate, and evaporated in vacuo to give the title compound (110mg, 100.3%) as an amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.98(3H, s), 5.69(1H, br s), 6.79(1H, d, J=8Hz), 6.89-7.02(3H, m), 7.59(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.45(1H, d, J=2Hz).
MS (ES+) : 326.06.

Example 76

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile

The title compound (57mg, 54.9%) was obtained as an amorphous powder from 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 75 (110mg, 0.338mmol) in a manner similar to that of Example 3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 3.98(3H, s), 6.80(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 308.04.

Example 77

5-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

To a solution of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde obtained by Example 71 (100mg, 0.322mmol) in dichloromethane (2mL) was added diethylaminosulfur trifluoride (62.3mg, 0.51mmol) at 0℃ under nitrogen, and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was partitioned between water and chloroform. The organic layer was separated, washed with 1mol/L

hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (toluene : ethyl acetate=9:1) and triturated with hexane to give the title compound (41mg, 38.3%) as an amorphous powder.

MP : 87-89°C.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.97(3H, s), 6.71(1H, t, J=52Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

MS (ES+) : 333.08.

Example 78-1

Diphenyl anilino(4-cyanophenyl)methylphosphonate

To a solution of 4-formylbenzonitrile (175g) in isopropyl acetate (2.1L) was added potassium fluoride (77.5mg) followed by addition of aniline (124g), and the mixture was heated to 60°C with stirring. To the mixture was added dropwise diphenyl phosphonate (469g) over 45min, and the mixture was heated at 60°C for additional 30min. To the mixture was added dropwise n-heptane (2.8L) over 2hrs, and the mixture was cooled to 15°C.

The resulting precipitate was collected by filtration, washed successively with water, 50% isopropyl acetate in n-heptane, and dried to give the title compound as crystals (494g, 84%).

^{1}H-NMR (300MHz, DMSO-d_6) : δ 5.70-6.00(1H, m), 6.61(1H, t, J=7Hz), 6.80-7.49(15H, m), 7.79-8.00(4H, m).

Example 78-2

4-[(4-Methoxyphenyl)acetyl]benzonitrile

To a mixture of diphenyl anilino(4-cyanophenyl)methylphosphonate obtained by Example 78-1 (493g) and 4-methoxybenzaldehyde (168g) in tetrahydrofuran (1.0L)

and 2-propanol (2.8L) was added potassium tert-butoxide (138g) in tetrahydrofuran (1.8L) over 6hrs. The mixture was stirred for additional 30min. To the mixture was added dropwise 2N hydrochloric acid (2.0L), and the mixture was heated at 45°C for 1hr.

The mixture was neutralized to pH 6 by adding 6N sodium hydroxide solution (700mL). The mixture was cooled to 5°C, and the resulting precipitate was collected by filtration, washed successively with 50% 2-propanol in cooled water, water, and dried to give the title compound as crystals (200g, 71%).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.78(3H, s), 4.23(2H, s), 6.87(2H, d, J=8.4Hz), 7.15(2H, d, J=8.4Hz), 7.74(2H, d, J=8.2Hz), 8.07(2H, d, J=8.2Hz).

Example 78-3

4-[Bromo(4-methoxyphenyl)acetyl]benzonitrile

To a solution of 4-[(4-methoxyphenyl)acetyl]benzonitrile obtained by Example 78-2 (3.0g, 11.9mmol) in tetrahydrofuran (30mL) was added pyridinium tribromide (3.82g, 11.9mmol) portionwise at room temperature under nitrogen, and the mixture was stirred at the same temperature for 1.5hrs.

The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with hexane to give the title compound (3.77g, 95.6%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.81(3H, s), 6.24(1H, s), 6.91(2H, d, J=8Hz), 7.44(2H, d, J=8Hz), 7.75(2H, d, J=8Hz), 8.06(2H, d, J=8Hz).

Example 78-4

2-(4-Cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

To a solution of 4-[bromo(4-methoxyphenyl)acetyl]benzonitrile obtained by Example 78-3 (500mg, 1.51mmol) in acetone were added acetoxyacetic acid (179mg, 1.51mmol) and cesium carbonate (493mg, 1.51mmol) at room temperature under nitrogen, and the mixture was stirred at the same temperature for 18hrs.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (337mg, 60.6%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.15(3H, s), 3.85(3H, s), 4.74(1H, d, J=16Hz), 4.82(1H, d, J=16Hz), 6.87-6.96(3H, m), 7.58(2H, d, J=9Hz), 7.68(2H, d, J=9Hz), 7.90(2H, d, J=9Hz).
MS (ES-) : 366.15.

Example 78-5
[4-(4-Cyanophenyl)-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate

The title compound (250mg, 78.8%) was obtained as an oil from 2-(4-cyanophenyl)-1-(4-methoxyphenyl)- 2-oxoethyl (acetyloxy)acetate obtained by Example 78-4 (335mg, 0.912mmol) and ammonium acetate (562mg, 7.3mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.19(3H, s), 3.86(3H, s), 5.25(2H, s), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.63(2H, d, J=8Hz), 7.71(2H, d, J=8Hz).
MS (ES+) : 349.03.

Example 79
4-[2-(Hydroxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]benzoni

trile

The title compound (100mg, 45.5%) was obtained as a powder from [4-(4-cyanophenyl)-5-(4- methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate obtained by Example 78-5 (250mg, 0.718mmol) in a manner similar to that of Example 70.

MP : 151-153℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.50(1H, t, J=5Hz), 3.87(3H, s), 4.84(2H, d, J=5Hz), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.70(2H, d, J=8Hz).

MS (ES+) : 307.03.

Example 80-1

4-[1-Bromo-2-(4-methoxyphenyl)-2-oxoethyl]benzonitrile

The title compound (2.09g, 106%) was obtained as a powder from 4-[2-(4-methoxyphenyl)-2-oxoethyl]- benzonitrile (1.5g, 5.97mmol) in a manner similar to that of Example 78-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.88(3H, s), 6.28(1H, s), 6.96(2H, d, J=8Hz), 7.67(4H, s), 7.98(2H, d, J=8Hz).

Example 80-2

1-(4-Cyanophenyl)-2-(4-methoxyphenyl)-2-oxoethyl methoxyacetate

The title compound (426mg, 82.9%) was obtained as an oil from 4-[1-bromo-2-(4-methoxyphenyl)-2- oxoethyl]benzonitrile obtained by Example 80-1 (500mg, 1.51mmol) and methoxyacetic acid (179mg, 1.51mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.85(3H, s), 4.17(1H, d, J=15Hz), 4.25(1H, d, J=15Hz), 6.90(2H, d, J=8Hz), 6.95(1H, s), 7.59(2H, d, J=8Hz), 7.66(2H, d, J=8Hz), 7.91(2H, d, J=8Hz).

MS (ES-) : 338.18.

Example 80-3

4-[2-(Methoxymethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]benzonitrile

The title compound (188mg, 47.1%) was obtained as crystals from 1-(4-cyanophenyl)-2-(4-methoxyphenyl)-2- oxoethyl methoxyacetate obtained by Example 80-2 (423mg, 1.51mmol) in a manner similar to that of Example 64-2.

MP : 85-86℃.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.53(3H, s), 3.86(3H, s), 4.62(2H, s), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.73(2H, d, J=8Hz).

MS (ES+) : 321.08.

Example 81-1

2-(4-Cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl methoxyacetate

The title compound (229mg, 89.1%) was obtained as an oil from 4-[bromo(4-methoxyphenyl)acetyl]- benzonitrile obtained by Example 78-3 (250mg, 0.757mmol) and methoxyacetic acid (89.4mg, 0.757mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.79(3H, s), 4.16(1H, d, J=15Hz), 4.25(1H, d, J=15Hz), 6.82(1H, s), 6.90(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 7.70(2H, d, J=8Hz), 7.96(2H, d, J=8Hz).

Example 81-2

4-[2-(Methoxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]benzonitrile

The title compound (47mg, 21.9%) was obtained as crystals from 2-(4-cyanophenyl)-1-(4-methoxyphenyl)- 2-oxoethyl methoxyacetate obtained by Example 81-1 (227mg, 0.669mmol) in a manner similar to

that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.52(3H, s), 3.86(3H, s), 4.60(2H, s), 6.94(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.80(2H, d, J=8Hz).
MS (ES+) : 321.10.

Example 82-1
2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

The title compound (1.26g, 100%) was obtained as an oil from 1-[4-(benzyloxy)phenyl]-2-bromo-2-(4-methoxyphenyl)ethanone obtained by Example 9-1 (1.24g, 2.81mmol) and acetoxyacetic acid (332mg, 2.81mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 3.78(3H, s), 4.72(1H, d, J=15Hz), 4.80(1H, d, J=15Hz), 5.08(2H, s), 6.85(1H, s), 6.87(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.30-7.43(7H, m), 7.89(2H, d, J=8Hz).

Example 82-2
[4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate

The title compound (1.2g, 99.5%) was obtained as an oil from 2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 82-1 (1.26g, 2.81mmol) and ammonium acetate (1.73g, 22.5mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.17(3H, s), 3.84(3H, s), 5.09(2H, s), 5.21(2H, s), 6.90(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.28-7.47(5H, m), 7.52(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

Example 83

[4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]met
hanol

The title compound (570mg, 52.7%) was obtained as an oil from [4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate obtained by Example 82-2 (1.2g, 2.79mmol) in a manner similar to that of Example 70.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.70(1H, br peak), 3.84(3H, s), 4.80(2H, s), 5.09(2H, s), 6.90(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.30-7.47(5H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).
MS (ES+) : 388.06.

Example 84
4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazole-2-carbal
dehyde

The title compound (438mg, 77.2%) was obtained as a powder from [4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 83 (570mg, 1.47mmol) in a manner similar to that of Example 71.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.12(2H, s), 6.91(2H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.50(5H, m), 7.60(2H, d, J=8Hz), 7.65(2H, d, J=8Hz), 9.76(1H, s).

Example 85
4-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-5-(4-methoxyphenyl)-1
,3-oxazole

The title compound (392mg, 76.5%) was obtained as a powder from 4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 84 (485mg, 1.26mmol) in a manner similar to that of Example 77.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.10(2H, s), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.29-7.49(5H, m), 7.53-7.61(4H, m).
MS (ES+) : 408.03.

Example 86
4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol

The title compound (279mg, 92.3%) was obtained as a powder from 4-[4-(benzyloxy)phenyl]-2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazole obtained by Example 85 (388mg, 0.952mmol) in a manner similar to that of Example 65.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.10(1H, br-s), 6.70(1H, t, J=53Hz), 6.85(2H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).
MS (ES-) : 316.25.

Example 87
2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanol

To a solution of 4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol obtained by Example 86 (120mg, 0.378mmol) in N,N-dimethylformamide (2mL) were added 2-chloroethanol (76.1mg, 0.946mmol), potassium iodide (157mg, 0.946mmol) and potassium carbonate (209mg, 1.51mmol) at room temperature, and the mixture was stirred at 75°C for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:3) to give the title compound (52.6mg, 38.5%) as an

amorphous powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.03(1H, t, J=7Hz), 3.85(3H, s), 3.94-4.03(2H, m), 4.13(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.51-7.60(4H, m).

Example 88

tert-Butyl 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethylcarbamate

To a solution of 4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol obtained by Example 86 (208mg, 0.656mmol), N-(tert-butoxycarbonyl)-2-aminoethanol (127mg, 0.787mmol) and diethyl azodicarboxylate (171mg, 0.983mmol) in anhydrous tetrahydrofuran (2mL) was added dropwise a solution of triphenylphosphine (258mg, 0.983mmol) in anhydrous tetrahydrofuran (4mL) at room temperature, and the mixture was stirred at the same temperature for 18hrs.

The mixture was evaporated in vacuo and the residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=3:1) to give the title compound (138mg, 45.7%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.55(2H, q, J=5Hz), 3.85(3H, s), 4.05(2H, t, J=5Hz), 5.00(1H, br peak), 6.70(1H, t, J=52Hz), 6.86-6.95(4H, m), 7.51-7.60(4H, m).

Example 89

2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanamine hydrochloride

The title compound (96mg, 81.9%) was obtained as an amorphous powder from tert-butyl 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethylcarbamate obtained by Example 88 (136mg, 0.295mmol) in a

manner similar to that of Example 17.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.24(2H, t, J=5Hz), 3.81(3H, s), 4.20(2H, t, J=5Hz), 7.01-7.10(4H, m), 7.30(1H, t, J=53Hz), 7.50(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 8.06(3H, br peak).
MS (ES+) : 361.09.

Example 90
N-(2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl] phenoxy}ethyl)urea

The title compound (70mg, 87.2%) was obtained as an amorphous powder from 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanamine hydrochloride obtained by Example 89 (79mg, 0.199mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.26-3.40(2H, m), 3.81(3H, s), 3.98(2H, t, J=5Hz), 5.54(2H, s), 6.18(1H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.30 (1H, t, J=52Hz), 7.46-7.55(4H, m).
MS (ES+) : 404.07.

Example 91-1
Benzyl 2-(4-bromophenyl)ethyl ether

To a slurry of sodium hydride (abt. 60% oil suspension, 4.58g) in N,N-dimethylformamide (150mL) was added dropwise 2-(4-bromophenyl)ethanol (20g) in N,N-dimethylformamide (50mL) at 0℃, and the mixture was stirred for 1hr at room temperature. To the mixture was added dropwise benzyl bromide (19.6g) at 0℃, and the mixture was stirred at room temperature for 6hrs.

The resulting mixture was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the title compound as a colorless oil (29.0g, 100%).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.88(2H, t, J=7Hz), 3.67(2H, t, J=7Hz), 4.52(2H, s), 7.11(2H, d, J=8Hz), 7.27-7.37(5H, m), 7.41(2H, d, J=8Hz).

Example 91-2

4-[2-(Benzyloxy)ethyl]benzaldehyde

To a solution of benzyl 2-(4-bromophenyl)ethyl ether obtained by Example 91-1 (29.0g) in dry tetrahydrofuran (300mL) was added dropwise n-butyllithium (1.57mol/L solution in hexanes, 66.5mL) at -78°C under nitrogen, and the mixture was stirred at -78°C for 1hr. To the mixture was added dropwise N,N-dimethylformamide (15.4mL).

After being stirred for 1.5hrs at -78°C, the mixture was warmed to room temperature, then poured into saturated aqueous ammonium chloride, and extracted with ether three times. The combined organic extracts were washed with water, brine, dried over anhydrous magnesium sulfate, and concentrated to give the title compound as a yellow oil (23.9g, 100%).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.02(2H, t, J=7Hz), 3.74(2H, t, J=7Hz), 4.53(2H, s), 7.37-7.27(5H, m), 7.41(2H, d, J=8Hz), 7.82(2H, d, J=8H), 10.00(1H, s).

Example 91-3

(2E)- and (2Z)-3-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-propenoic acid

A mixture of 4-[2-(benzyloxy)ethyl]benzaldehyde obtained by Example 91-2 (23.9g) and 4-methoxyphenylacetic acid (16.5g) in acetic anhydride (30mL) and triethylamine (17mL) was heated under reflux with stirring for 8hrs.

After cooling, the mixture was concentrated, and partitioned between 1N sodium hydroxide solution (500mL) and ether. The ether layer was discarded. The aqueous layer was acidified with 1mol/L

hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried to give the title compound as crystals (19.8g, 51.2%).

^{1}H-NMR (300MHz, DMSO-d_6, a mixture of E- and Z-isomers) : δ 2.78(2H×0.76, t, J=7Hz), 2.86(2H×0.24, t, J=7Hz), 3.59(2H×0.76, t, J=7Hz), 3.66(2H×0.24, t, J=7Hz), 3.78(3H×0.76, s), 3.78(3H×0.24, s), 4.44(2H×0.76, s), 4.49(2H×0.24, s), 6.91-7.69(14H, m).
MS(ESI) : 389.09(M+H), 387.22(M-H).

Example 91-4
2-{4-[2-(Benzyloxy)ethyl]phenyl}-1-(4-methoxyphenyl)ethanone

To a solution of (2E)- and (2Z)-3-{4-[2-(benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-propenoic acid obtained by Example 91-3 (19.4g) in 1,4-dioxane (200mL) was added triethylamine (7.66mL) followed by addition of diphenylphosphoryl azide (15.1g). The mixture was heated at 100°C with stirring for 30min. To the mixture was added dropwise 50% acetic acid in water (200mL), and the mixture was heated at 100°C for 1.5hrs.

After cooling, the mixture was concentrated, and the residue was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was dissolved in ethanol with stirring to give the title compound as crystals (12.3g, 68.3%).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.90(2H, t, J=7Hz), 3.67(2H, t, J=7Hz), 3.86(3H, s), 4.20(2H, s), 4.51(2H, s), 6.92(2H , d, J=9Hz), 7.18(4H , s), 7.24-7.34(5H , m), 7.99(2H, d, J=9Hz).
MS(ESI) : 361.13.

Example 91-5
2-{4-[2-(Benzyloxy)ethyl]phenyl}-2-bromo-1-(4-methoxyphenyl)ethanone

The title compound (4.3g, 100%) was obtained as an oil from 2-{4-[2-(benzyloxy)ethyl]phenyl}-1-(4- methoxyphenyl)ethanone obtained by Example 91-4 (3.5g, 9.71mmol) and pyridinium tribromide (3.42g, 10.7mmol) in a manner similar to that of Example 78-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.90(2H, t, J=7Hz), 3.66(2H, t, J=7Hz), 3.85(3H, s), 4.50(2H, s), 6.35(1H, s), 6.90(2H, d, J=8Hz), 7.15-7.35(7H, m), 7.44(2H, d, J=8Hz), 7.96 (2H, d, J=8Hz).

Example 91-6
1-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

The title compound (4.2g, 90.2%) was obtained as an oil from 2-{4-[2-(benzyloxy)ethyl]phenyl}-2-bromo-1-(4-methoxyphenyl)ethanone obtained by Example 91-5 (4.3g, 9.79mmol) and acetoxyacetic acid (1.16g, 9.79mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 2.89(2H, t, J=7Hz), 3.64(2H, t, J=7Hz), 3.82(3H, s), 4.49(2H, s), 4.73(1H, d, J=15Hz), 4.80(1H, d, J=15Hz), 6.81-6.90(3H, m), 7.18-7.32(7H, m), 7.36(2H, d, J=8Hz), 7.90(2H, d, J=8Hz).

Example 91-7
[5-{4-[2-(Benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

To a solution of 1-{4-[2-(benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 91-6 (4.2g, 8.83mmol) in acetic acid (40mL) was added ammonium acetate (5.44g, 70.6mmol) at room temperature, and the mixture was heated to reflux with stirring for 4hrs.

After cooling, the reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate.

After evaporation of solvent, the residue was dissolved in methanol (20mL). To a solution was added potassium carbonate (610mg) at room temperature, and the mixture was stirred at the same temperature for 1hr.

The reaction mixture was evaporated in vacuo, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (chloroform) to give the title compound (2.67g, 72.8%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.94(2H, t, J=7Hz), 3.70(2H, t, J=7Hz), 3.84(3H, s), 4.53(2H, s), 4.80(2H, s), 6.90(2H, d, J=8Hz), 7.15-7.39(7H, m), 7.50(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

Example 92

5-{4-[2-(Benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde

The title compound (605mg, 22.8%) was obtained as an oil from [5-{4-[2-(benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 91-7 (2.37g, 6.43mmol) in a manner similar to that of Example 71.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.96(2H, t, J=7Hz), 3.73(2H, t, J=7Hz), 3.87(3H, s), 4.53(2H, s), 6.95(2H, d, J=8Hz), 7.20-7.40(7H, m), 7.55-7.67(4H, m), 9.79(1H, s).

Example 93

5-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole

The title compound (483mg, 75.8%) was obtained as an oil from 5-{4-[2-(benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 92 (605mg, 1.46mmol) in a manner similar to that of Example 77.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.99(2H, t, J=7Hz), 3.71(2H, t, J=7Hz), 3.85(3H, s), 4.54(2H, s), 6.70(1H, t, J=53Hz), 6.91(2H, d, J=8Hz), 7.19-7.37(7H, m), 7.50-7.63(4H, m).

Example 94

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethanol

The title compound (305mg, 80%) was obtained as a powder from 5-{4-[2-(benzyloxy)ethyl]phenyl}-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 93 (481mg, 1.1mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(1H, t, J=7Hz), 2.91(2H, t, J=7Hz), 3.85(3H, s), 3.90(2H, q, J=7Hz), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.54-7.62(4H, m).
MS (ES+) : 346.14.

Example 95

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl methanesulfonate

The title compound (308mg, 100%) was obtained as an oil from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethanol obtained by Example 94 (250mg, 0.724mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.92(3H, s), 3.09(2H, t, J=7Hz), 3.85(3H, s), 4.45(2H, t, J=7Hz), 6.70(1H, t, J=53Hz), 6.93(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).

Example 96

2-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (365mg, 107%) was obtained as a powder from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl methanesulfonate obtained by Example 95 (305mg, 0.72mmol) and potassium phthalimide (200mg, 1.08mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.03(2H, t, J=7Hz), 3.85(3H, s), 3.95(2H, t, J=7Hz), 6.69(1H, t, J=53Hz), 6.90(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.49-7.58(4H, m), 7.68-7.74(2H, m), 7.80-7.86(2H, m).

Example 97

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine

The title compound (300mg, 115%) was obtained as an oil from 2-(2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 96 (360mg, 0.759mmol) in a manner similar to that of Example 44.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.68-2.90(4H, m), 3.85(3H, s), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=9Hz), 7.15-7.30(2H, m), 7.44-7.64(4H, m).

Example 98

N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)methanesulfonamide

The title compound (78mg, 42.4%) was obtained as an oil from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine obtained by Example 97 (150mg, 0.434mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.90(3H, s), 2.92(2H, t, J=7Hz), 3.44(2H, t, J=7Hz), 3.86(3H, s), 4.22(1H, t, J=6Hz), 6.71(1H, t, J=53Hz), 6.94(2H, d, J=8Hz), 7.25(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES-) : 421.19.

Example 99
N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)urea

The title compound (32mg, 19%) was obtained as a powder from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine obtained by Example 97 (150mg, 0.436mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 2.73(2H, t, J=7Hz), 3.22(2H, q, J=7Hz), 3.80(3H, s), 5.44(2H, s), 5.95(1H, t, J=6Hz), 7.00(2H, d, J=8Hz), 7.31(1H, t, J=53Hz), 7.33(2H, d, J=8Hz), 7.46-7.56(4H, m).
MS (ES+) : 388.15.

Example 100-1
2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)ethanone

1.56M n-Butyllithium in hexane (134mL, 209mmol) was added dropwise to a solution of 5-bromo-2-methoxypyridine (36.3g, 193mmol) in tetrahydrofuran (340mL) at -78°C and the suspension stirred at the same temperature for 1hr. 2-[4-(Benzyloxy)phenyl]-N-methoxy-N-methylacetamide (55.1g, 193mmol) in tetrahydrofuran (340mL) was then added and stirring

continued for a further 2.5hrs.

The mixture was allowed to 3℃ and then it was poured into NH_4Cl solution. The mixture was extracted with ethyl acetate (1000mL) and the organic extract was washed with brine. The organic extract was dried (magnesium sulfate) and the solvent was removed to give the title compound as solid. The solid was washed with isopropyl alcohol - isopropyl ether to give the title compound as white crystals.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.99(3H, s), 4.16(2H, s), 5.04(2H, s), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.18(2H, d, J=8Hz), 7.30-7.43(5H, m), 8.16(1H, dd, J=8,2Hz), 8.85(1H, d, J=2Hz).
MS (ES+) : 334.10.

Example 100-2

2-[4-(Benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone

The title compound as an oil (1.87g, 100%) was obtained from 2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3- pyridinyl)ethanone obtained by Example 100-1 (1.5g, 4.5mmol) in a manner similar to that of Example 78-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 4.00(3H, s), 5.06(2H, s), 6.28(1H, s), 6.78(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.50(7H, m), 8.16(1H, dd, J=9,2Hz), 8.81(1H, d, J=2Hz).

Example 100-3

1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-methylpropanoate

The title compound (819mg, 43%) was obtained as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 100-2 (1.87g, 4.54mmol) and isobutyric acid (400mg, 4.54mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.19(3H, d, J=7Hz), 1.26(3H, d, J=7Hz), 2.63-2.78(1H, m), 3.96(3H, s), 5.03(2H, s), 6.66(1H, s), 6.72(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.26-7.43(7H, m), 8.10(1H, dd, J=8,2Hz), 8.78(1H, d, J=2Hz).

Example 100-4

5-{5-[4-(Benzyloxy)phenyl]-2-isopropyl-1,3-oxazol-4-yl}-2-methoxypyridine

The title compound (562mg, 71.9%) was obtained as a powder from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3- pyridinyl)-2-oxoethyl 2-methylpropanoate obtained by Example 100-3 (819mg, 1.95mmol) and ammonium acetate (1.2g, 15.6mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.09-3.21(1H, m), 3.96(3H, s), 5.09(2H, s), 6.75(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.51(7H, m), 7.81(1H, dd, J=9,2Hz), 8.40(1H, d, J=2Hz).

Example 101

4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

The title compound (410mg, 97.6%) was obtained as a powder from 5-{5-[4-(benzyloxy)phenyl]-2-isopropyl-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 100-4 (542mg, 1.35mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.34(6H, d, J=7Hz), 3.05-3.20(1H, m), 3.87(3H, s), 6.82(2H, d, J=9Hz), 6.86(1H, d, J=9Hz), 7.34(2H, d, J=9Hz), 7.80(1H, dd, J=9,2Hz), 8.32(1H, d, J=2Hz), 9.91(1H, br peak).
MS (ES+) : 311.22.

Example 102

2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phen

oxy}ethanol

The title compound (385mg, 84.3%) was obtained as a powder from 4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)- 1,3-oxazol-5-yl]phenol obtained by Example 101 (400mg, 1.29mmol) and chloroethanol (623mg, 7.73mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 2.02(1H, t, J=6Hz), 3.09-3.22(1H, m), 3.96(3H, s), 3.96-4.01(2H, m), 4.10(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.91(2H, d, J=9Hz), 7.48(2H, d, J=9Hz), 7.81(1H, dd, J=9,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 355.24.

Example 103

2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (400mg, 99.9%) was obtained as an oil from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 102 (328mg, 0.926mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.43(6H, d, J=7Hz), 3.11(3H, s), 3.11-3.22(1H, m), 3.96(3H, s), 4.23-4.30(2H, m), 4.54-4.61(2H, m), 6.76(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).

Example 104

2-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (355mg, 79.4%) was obtained as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 103 (400mg, 0.925mmol) and potassium phthalimide

(257mg, 1.39mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.20(1H, m), 3.94(3H, s), 4.12(2H, t, J=5Hz), 4.25(2H, t, J=5Hz), 6.73(1H, d, J=9Hz), 6.86(2H, d, J=9Hz), 7.43(2H, d, J=9Hz), 7.69-7.80(3H, m), 7.80-7.93(2H, m), 8.36(1H, d, J=2Hz).
MS (ES+) : 484.17.

Example 105
2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (327mg, 127%) was obtained as an an oil from 2-(2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 104 (353mg, 0.73mmol) in a manner similar to that of Example 36.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.05-3.21(3H, m), 3.95(3H, s), 4.00(2H, t, J=5Hz), 6.75(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.81(1H, dd, J=9,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 354.21.

Example 106
N-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (67mg, 54.9%) was obtained as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 105 (100mg, 0.283mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.04(3H, s), 3.10-3.21(1H, m), 3.56(2H, q, J=5Hz), 3.96(3H, s), 4.12(2H, t, J=5Hz),

4.76(1H, br peak), 6.75(1H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.81(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 432.19.

Example 107
N-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (121mg, 61.3%) was obtained as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 105 (176mg, 0.498mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.09-3.21(1H, m), 3.61(2H, q, J=5Hz), 3.95(3H, s), 4.06(2H, t, J=5Hz), 4.42(2H, br-s), 5.00(1H, br peak), 6.75(1H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 397.18.

Example 108-1
2-[4-(Benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone

The title compound (10g, 101%) was obtained as an oil from 2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)- ethanone (8.0g, 24.1mmol) in a manner similar to that of Example 78-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 5.05(2H, s), 6.37(1H, s), 6.90(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.27-7.50(7H, m), 7.96(2H, d, J=9Hz).

Example 108-2
1-[4-(Benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl cyclopropanecarboxylate

The title compound (1.68g, 83%) was obtained as an oil from

2-[4-(benzyloxy)phenyl]-2-bromo-1-(4- methoxyphenyl)ethanone obtained by Example 108-1 (2.0g, 4.86mmol) and cyclopropanecarboxylic acid (419mg, 4.86mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 0.85-0.96(2H, m), 1.01-1.11(2H, m), 1.71-1.85(1H, m), 3.82(3H, s), 5.03(2H, s), 6.80(1H, s), 6.86(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.26-7.44(7H, m), 7.91(2H, d, J=9Hz).

Example 108-3
5-[4-(Benzyloxy)phenyl]-2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazole

The title compound (1.28g, 80.8%) was obtained as an oil from 1-[4-(benzyloxy)phenyl]-2-(4- methoxyphenyl)-2-oxoethyl cyclopropanecarboxylate obtained by Example 108-2 (1.66g, 3.99mmol) and ammonium acetate (2.46g, 31.9mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.19(2H, m), 2.05-2.17(1H, m), 3.83(3H, s), 5.08(2H, s), 6.87(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.30-7.49(7H, m), 7.54(2H, d, J=9Hz)
MS (ES+) : 398.18

Example 109
4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (912mg, 94.4%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazole Example 108-3 (1.25g, 3.14mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.19(2H, m), 2.05-2.18(1H, m), 3.82(3H, s), 5.13(1H, br-s), 6.80(2H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.40(2H, d, J=9Hz), 7.53(2H, d, J=9Hz).

MS (ES+) : 308.18.

Example 110

2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy} ethanol

The title compound (765mg, 74.3%) was obtained as a powder from 4-[2-cyclopropyl-4-(4-methoxyphenyl)- 1,3-oxazol-5-yl]phenol obtained by Example 109 (900mg, 2.93mmol) and 2-chloroethanol (1.41g, 17.6mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 0.97-1.13(4H, m), 2.18-2.21(1H, m), 3.71(2H, q, J=5Hz), 3.77(3H, s), 4.00(2H, t, J=5Hz), 4.89(1H, t, J=5.5Hz) ,6.93(2H, d, J=9Hz), 6.98(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.95(2H, d, J=9Hz).
MS (ES+) : 352.20.

Example 111

2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy} ethyl methanesulfonate

The title compound (308 mg, 100%) was obtained as an oil from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 110 (250mg, 0.711mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.12(2H, m), 1.12-1.20(2H, m), 2.06-2.19(1H, m), 3.10(3H, s), 3.83(3H, s), 4.23-4.30(2H, m), 4.55-4.61(2H, m), 6.83-6.91(4H, m), 7.46(2H, d, J=9Hz), 7.51(2H, d, J=9Hz).

Example 112

2-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (237mg, 68.8%) was obtained as a powder from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 111 (308mg, 0.717mmol) and potassium phthalimide (199mg, 1.08mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 0.97-1.09(4H, m), 2.06-2.21(1H, m), 3.76(3H, s), 3.96(2H, t, J=6Hz), 4.25(2H, t, J=6Hz), 6.89-6.99(4H, m), 7.38(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.81-7.94(4H, m).
MS (ES+) : 481.17.

Example 113
2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (201mg, 119%) was obtained as an oil from 2-(2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 112 (233mg, 0.482mmol) in a manner similar to that of Example 36.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.20(2H, m), 2.05-2.18(1H, m), 3.09(2H, t, J=5Hz), 3.93(3H, s), 4.01(2H, d, J=5Hz), 6.81-6.92(4H, m), 7.45(2H, d, J=9Hz), 7.53(2H, d, J=9Hz).

Example 114
N-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (64 mg, 69.8%) was obtained as an oil from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 113 (75mg, 0.214mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.01-1.11(2H, m), 1.11-1.20(2H, m),

2.04-2.18(1H, m), 3.03(3H, s), 3.56(2H, q, J=5Hz), 3.80(3H, s), 4.12(2H, t, J=5Hz), 4.75(1H, br peak), 6.85(2H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.52(2H, d, J=9Hz).

Example 115

N-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (94mg, 66.4%) was obtained as a powder from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 113 (126mg, 0.36mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 0.96-1.11(4H, m), 2.09-2.20(1H, m), 3.26-3.36(2H, m), 3.76(3H, s), 3.96(2H, t, J=5Hz), 5.564(2H, s), 6.66(1H, t, J=5Hz), 6.94(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.45(2H, d, J=9Hz).

MS (ES+) : 394.21.

Example 116-1

1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl cyclopropanecarboxylate

The title compound (1.72g, 93.8%) was obtained as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone (1.85g, 4.39mmol) and cyclopropanecarboxylic acid (378mg, 4.39mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 0.85-0.99(2H, m), 1.04-1.14(2H, m), 1.71-1.85(1H, m), 3.96(3H, s), 5.04(2H, s), 6.70(1H, s), 6.73(1H, d, J=9Hz), 6.97(2H, d, J=9Hz), 7.28-7.45(7H, m), 8.10(1H, dd, J=9,2Hz), 8.78(1H, d, J=2Hz).

MS (ES+) : 418.18.

Example 116-2

5-{5-[4-(Benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine

The title compound (1.14g, 69.4%) was obtained as a powder from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl cyclopropanecarboxylate obtained by Example 116-1 (1.72g, 4.12mmol) and ammonium acetate (2.54g, 33mmol) in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.03-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.19(1H, m), 3.95(3H, s), 5.08(2H, s), 6.74(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.30-7.48(7H, m), 7.80(1H, dd, J=8,2Hz), 8.39(1H, d, J=2Hz).

MS (ES+) : 399.17.

Example 117

4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

The title compound (710mg, 83.4%) was obtained as a powder from 5-{5-[4-(benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 116-2 (1.1g, 2.76mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.01-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.18(1H, m), 3.95(3H, s), 6.16(1H, br peak), 6.75(1H, d, J=9Hz), 6.81(2H, d, J=9Hz), 7.38 (2H, d, J=9Hz), 7.84(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).

MS (ES+) : 309.14.

Example 118

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (575mg, 71.9%) was obtained as a powder from 4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol obtained by Example 117 (700mg, 2.27mmol) and 2-chloroethanol (1.1 g, 13.6 mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.02-1.11(2H, m), 1.11-1.20(2H, m), 2.02(1H, t, J=6Hz), 2.06-2.17(1H, m), 3.95(3H, s), 3.98(2H, t, J=5Hz), 4.10(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.79(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 353.19.

Example 119

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (310mg, 102%) was obtained as an oil from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 118 (250mg, 0.709mmol) in a manner similar to that of Example 34.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.04-1.13(2H, m), 1.13-1.21(2H, m), 2.08-2.20(1H, m), 3.11(3H, s), 3.97(3H, s), 4.22-4.30(2H, m), 4.55-4.61(2H, m), 6.76(1H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 431.11.

Example 120

2-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (256mg, 73.8%) was obtained as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 119 (310mg, 0.72mmol) and

potassium phthalimide (200mg, 1.08mmol) in a manner similar to that of Example 35.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.00-1.12(4H, m), 2.11-2.23(1H, m), 3.86(3H, s), 3.97(2H, t, J=5Hz), 4.26(2H, t, J=5Hz), 6.84(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.39(2H, d, J=9Hz), 7.75(1H, dd, J=9,2Hz), 7.80-7.94(4H, m), 8.28(1H, d, J=2Hz).
MS (ES+) : 482.16.

Example 121
2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (220mg, 121%) was obtained as an oil from 2-(2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 120 (250mg, 0.519mmol) in a manner similar to that of Example 36.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.19(1H, m), 3.10(2H, t, J=5Hz), 3.95(3H, s), 4.00(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.79(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 352.22.

Example 122
N-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (57mg, 51.8%) was obtained as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 121 (90mg, 0.256mmol) in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.03-1.12(2H, m), 1.12-1.21(2H, m),

2.06-2.19(1H, m), 3.04(3H, s), 3.50-3.60(2H, m), 3.95(3H, s), 4.11(2H, t, J=5Hz), 4.76(1H, br peak), 6.75(1H, d, J=9Hz), 6.86(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.80(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 430.10.

Example 123
N-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (63mg, 43.2%) was obtained as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 121 (130mg, 0.37mmol) in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 0.99-1.15(4H, m), 2.12-2.24(1H, m), 3.29-3.39(2H, m), 3.87(3H, s), 3.97(2H, t, J=5Hz), 5.54(2H, br-s), 6.16(1H, t, J=5Hz), 6.86(1H, d, J=9Hz), 7.01(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.78(1H, dd, J=9,2Hz), 8.31(1H, d, J=2Hz).
MS (ES+) : 395.17.

Example 124-1
1-[4-(Benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

The title compound (8.75g, 100%) was obtained as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone (8.3g, 19.5mmol) and acetoxyacetic acid (2.3g, 19.5 mmol) in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 3.82(3H, s), 4.72(1H, d, J=16Hz), 4.80(1H, d, J=16Hz), 5.02(2H, s), 6.80-6.90(3H, m), 6.95(2H, d, J=9Hz), 7.28-7.43(7H, m), 7.89(2H, d, J=9Hz).

Example 124-2
[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]met

hanol

The title compound (4.88g, 64.6%) was obtained as a powder from 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 124-1 (8.75g, 19.5mmol) in a manner similar to that of Example 91-7.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 4.78(2H, s), 5.08(2H, s), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.46(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

Example 125
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde

The title compound (3.08g, 63.4%) was obtained as a powder from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 124-2 (4.88g, 12.6mmol) in a manner similar to that of Example 71.

H-NMR (300MHz, $CDCl_3$) : δ 3.87(3H, s), 5.11(2H, s), 6.95(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.30-7.50(5H, m), 7.60(2H, d, J=9Hz), 7.65(2H, d, J=9Hz), 9.76(1H, s).

Example 126
1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol

The title compound (150mg, 26.9%) was obtained as an oil from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (500mg, 1.3mmol) and isopropylmagnesium bromide (0.7M solution in tetrahydrofuran, 2.78mL) in a manner similar to that of Example 72.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 0.98-1.07(6H, m), 2.15-2.34(1H, m),

3.83(3H, s), 4.59(1H, br peak), 5.08(2H, s), 6.90(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.29-7.45(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 430.19.

Example 127

4-[2-(1-Hydroxy-2-methylpropyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (231mg, 108%) was obtained as an oil from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol obtained by Example 126 (270mg, 0.629mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 0.99-1.08(6H, m), 2.15-2.31(1H, m), 2.74(1H, d, J=7Hz), 3.83(3H, s), 4.60(1H, t, J=7Hz), 5.41(1H, s), 6.82(2H, d, J=9Hz), 7.90(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 340.19.

Example 128

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol

The title compound (126mg, 48.9%) was obtained as an oil from 4-[2-(1-hydroxy-2-methylpropyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 127 (228mg, 0.672mmol) and 2-chloroethanol (325mg, 4.03mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.10(6H, m), 2.00(1H, t, J=6Hz), 2.19-2.33(1H, m), 2.65(1H, d, J=6Hz), 3.84(3H, s), 3.96(2H, q, J=5Hz), 4.10(2H, t, J=5Hz), 4.60(1H, t, J=6Hz), 6.85-6.95(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 384.18.

Example 129

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

The title compound (17mg, 13.6%) was obtained as an oil from 1-[5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol obtained by Example 128 (126mg, 0.329mmol) in a manner similar to that of Example 71.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.29(6H, d, J=7Hz), 1.99(1H, t-like), 3.70-3.83(1H, m), 3.86(3H, s), 3.95-4.04(2H, m), 4.12(2H, t, J=5Hz), 6.88-6.99(4H, m), 7.58(2H, d, J=9Hz), 7.62(2H, d, J=9Hz).
MS (ES+) : 382.13.

Example 130

1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol

The title compound (143mg, 24.9%) was obtained as an oil from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (500mg, 1.3mmol) and isobutylmagnesium bromide (2M solution in diethyl ether, 0.78mL) in a manner similar to that of Example 72.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00(6H, d, J=7Hz), 1.74-1.99(3H, m), 2.50(1H, d, J=6Hz), 3.84(3H, s), 4.84-4.96(1H, m), 5.09(2H, s), 6.89(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.28-7.46(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 444.21.

Example 131

4-[2-(1-Hydroxy-3-methylbutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-

yl]phenol

The title compound (112mg, 99.7%) was obtained as an oil from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol obtained by Example 130 (141mg, 0.318mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.00(6H, d, J=7Hz), 1.76-1.96(3H, m), 2.59(1H, br peak), 3.83(3H, s), 4.85-4.95(1H, m), 5.37(1H, br peak), 6.81(2H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).
MS (ES+) : 354.19.

Example 132
1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol

The title compound (118mg, 95.4%) was obtained as an oil from 4-[2-(1-hydroxy-3-methylbutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 131 (110mg, 0.311mmol) and 2-chloroethanol (150mg, 1.87mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.01(6H, d, J=7Hz), 1.75-1.96(3H, m), 2.05(1H, br peak), 2.62(1H, br peak), 3.84(3H, s), 3.94-4.02(2H, m), 4.11(2H, t, J=5Hz), 4.90(1H, br peak), 6.85-6.95(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 398.20.

Example 133
1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

The title compound (42.5mg, 36.8%) was obtained as an oil from

1-[5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol obtained by Example 132 (116mg, 0.292mmol) in a manner similar to that of Example 71.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.04(6H, d, J=7Hz), 2.00(1H, t-like, J=5Hz), 2.30-2.46(1H, m), 3.00(2H, d, J=7Hz), 3.86(3H, s), 3.95-4.04(2H, m), 4.12(2H, t, J=5Hz), 6.88-6.99(4H, m), 7.59(2H, d, J=9Hz), 7.62(2H, d, J=9Hz).
MS (ES+) : 396.19.

Example 134
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid

The title compound (1.05g, 100%) was obtained as an amorphous from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (1.0g, 2.59mmol) in a manner similar to that of Example 74.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.78(3H, s), 5.14(2H, s), 6.98(2H, d, J=9Hz), 7.10(2H, d, J=9Hz), 7.30-7.54(9H, m).
MS (ES-) : 400.19.

Example 135
5-[4-(Benzyloxy)phenyl]-N,N-diethyl-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (132mg, 44.1%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid obtained by Example 134 (263mg, 0.655mmol) and diethylamine (57.5mg, 0.786mmol) in a manner similar to that of Example 75.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.26(3H, t, J=7Hz), 1.35(3H, t), 3.57(2H,

q, J=7Hz), 3.85(3H, s), 3.91(2H, q, J=7Hz), 5.09(2H, s), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.30-7.46(5H, m), 7.54-7.64(4H, m).

Example 136

N,N-Diethyl-5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (95mg, 91.1%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-N,N-diethyl-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 135 (130mg, 0.285mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.30(3H, t, J=7Hz), 1.39(3H, t, J=7Hz), 3.61(2H, q, J=7Hz), 3.85(3H, s), 4.05(2H, q, J=7Hz), 6.91(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.55-7.66(3H, m).
MS (ES+) : 367.20.

Example 137

N,N-Diethyl-5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (58mg, 57.5%) was obtained as a powder from N,N-diethyl-5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 136 (90mg, 0.246mmol) and 2-chloroethanol (119mg, 1.47mmol) in a manner similar to that of Example 87.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.16(3H, t, J=7Hz), 1.27(3H, t, J=7Hz), 3.46(2H, q, J=7Hz), 3.66-3.82(7H, m), 4.04(2H, t, J=5Hz), 4.90(1H, t, J=5Hz), 7.00(2H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.46-7.55(4H, m).
MS (ES+) : 411.19.

Example 138

1-{[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine

The title compound (185mg, 49.5%) was obtained as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid obtained by Example 134 (320mg, 0.797mmol) and piperidine (81.5mg, 0.957mmol) in a manner similar to that of Example 75.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.61-1.78(6H, m), 3.69-3.79(2H, m), 3.84(3H, s), 4.04-4.13(2H, m), 5.09(2H, s), 6.91(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.30-7.48(5H, m), 7.54-7.64(4H, m).
MS (ES+) : 469.20.

Example 139
4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol

The title compound (138mg, 94.9%) was obtained as a powder from 1-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine obtained by Example 138 (180mg, 0.384mmol) in a manner similar to that of Example 31.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.64-1.76(6H, m), 3.72-3.82(2H, m), 3.84(3H, s), 4.16-4.26(2H, m), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.24(1H, s), 7.45(2H, d, J=9Hz), 7.49(2H, d, J=9Hz).
MS (ES-) : 377.28.

Example 140
2-{4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (96mg, 66.1%) was obtained as a powder from 4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol obtained by Example 139 (130mg, 0.344mmol) and 2-chloroethanol (166mg, 2.06mmol) in a

manner similar to that of Example 87.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.53-1.72(6H, m), 3.63(2H, t, J=5.5Hz), 3.72(2H, q, J=5Hz), 3.79(3H, s), 3.94(2H, t, J=5.5Hz), 4.04(2H, t, J=5Hz), 4.90(1H, t, J=5.5Hz), 7.00(2H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.46-7.55(4H, m).
MS (ES+) : 423.15.

Example 141-1
Ethyl {[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}(oxo)acetate

The title compound (3.0g, 103%) was obtained from 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 30-5 in a manner similar to that of Example 1-1.

^{1}H-NMR (300MHz,$CDCl_3$) : δ 1.37(3H, t, J=7Hz), 3.88(3H, s), 4.35(2H, q, J=7Hz), 5.10(2H, s), 6.41(1H, d, J=7Hz), 6.67(1H, d, J=8Hz), 6.97(2H, d, J=8Hz), 7.31-7.40(5H, m), 7.56(1H, dd, J=8,2Hz), 7.94(2H, d, J=8Hz), 8.27(1H, d, J=2Hz), 8.55(1H, d, J=7Hz).

Example 141-2
Ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate

The title compound was obtained (2.3g, 82.6%) from ethyl {[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 141-1 in a manner similar to that of Example 9-5.

^{1}H-NMR (300MHz,$CDCl_3$) : δ 1.46(3H, t, J=7Hz), 3.97(3H, s), 4.52(2H, q, J=7Hz), 5.10(2H, s), 6.79(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.32-7.46(5H, m), 7.59(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

MS (ES+) : 431.17.

Example 142

5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

To a solution of ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate obtained by Example 141-2 (2.18g, 5.06mmol) in 80 mL of 1,4-dioxane at 0℃ was added 2M NH_3 in methanol (25mL, 50.6mmol). The clear solution was stirred for 30min at the same temperature and ammonia gas was bubbled for 5min. The reaction mixture was allowed to warm to room temperature and stirred for 3hrs.

The solution was evaporated to give the title compound (2.1g, quant.) as white crystals.

^{1}H-NMR (300MHz,$CDCl_3$) : δ 3.98(3H, s), 5.10(2H, s), 5.75(1H, br-s), 6.79(1H, d, J=8Hz), 6.97(1H, br-s), 7.00(2H, d, J=8Hz), 7.34-7.45(5H, m), 7.59(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.45(1H, d, J=2Hz).
MS (ES+) : 402.13.

Example 143

5-(4-Hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

The title compound was obtained (1.7g, 99.6%) from 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 142 in a manner similar to that of Example 65.

^{1}H-NMR (300MHz,DMSO-d_6) : δ 3.89(3H, s), 6.87(2H, d, J=8Hz), 6.92(1H, d, J=8Hz), 7.44(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 7.94(1H, br-s), 8.31(1H, br-s), 8.38(1H, d, J=2Hz).
MS (ES+) : 312.15.

Example 144

tert-Butyl 2-{4-[2-(aminocarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

The title compound was obtained (2.1g, 98.5%) from 5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 143 in a manner similar to that of Example 13.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.55(2H, m), 3.98(3H, s), 4.05(2H, t, J=5Hz), 5.02(1H, br), 5.83(1H, br-s), 6.79(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 6.99(1H, br-s), 7.58(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).

MS (ES+) : 455.08.

Example 145

tert-Butyl 2-{4-[2-cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

The title compound was obtained (1.4g, 69.4%) from tert-butyl 2-{4-[2-(aminocarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate obtained by Example 144 in a manner similar to that of Example 23.

^{1}H-NMR (300MHz,$CDCl_3$) : δ 1.46(9H, s), 3.56(2H, m), 3.98(3H, s), 4.07(2H, t, J=5Hz), 4.98(1H, br), 6.80(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.80(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

MS (ES+) : 437.09.

Example 146

5-[4-(2-Aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile

The title compound was obtained (1.3g, 108%) from tert-butyl

2-{4-[2-cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate obtained by Example 145 in a manner similar to that of Example 17.

^{1}H-NMR (300MHz,$CDCl_3$) : δ 3.10-3.14(2H, m), 3.89(1H, br-s), 3.97(3H, s), 4.03(2H, m), 4.28(1H, br), 6.78(1H, m), 6.98(2H, m), 7.54(2H, dd, J=8,2Hz), 7.80(1H, m), 8.43(1H, s).
MS (ES+) : 337.13.

Example 147
N-(2-{4-[2-Cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was obtained (20mg, 9.2%) from 5-[4-(2-aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile obtained by Example 146 in a manner similar to that of Example 38.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.55-3.61(2H, m), 3.98(3H, s), 4.16(2H, t, J=5Hz), 4.83(1H, br-t, J=5Hz), 6.81(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 415.01.

Example 148
N-(2-{4-[2-Cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained as crystals (55mg, 79.7%) from 5-[4-(2-aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile obtained by Example 146 in a manner similar to that of Example 18.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 3.30-3.39(2H, m), 3.90(3H, s), 4.01(2H, t, J=5Hz), 5.55(2H, s), 6.18(1H, br-t, J=5Hz), 6.94(1H, d, J=8Hz),

7.10(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.85(1H, dd, J=8,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 380.09.

Example 149-1
1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-hydroxy-2-methylpropanoate

The title compound (1.32g, 51.7%) was obtained from 2-(4-methoxyphenyl)-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone and 2-hydroxy-2-methylpropionic acid in a manner similar to that of Example 78-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.48(3H, s), 1.59(3H, s), 1.67(1H, br-s), 3.79(3H, s), 3.96(3H, s), 6.72(1H, s), 6.74(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.37(2H, d, J=8.8Hz), 8.09(1H, dd, J=8.8,2.6Hz), 8.77(1H, d, J=2.6Hz).
MS (ES+) : 360.20.

Example 149-2
2-[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-2-propanol

The title compound (175mg, 14%) was obtained from 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-hydroxy-2-methylpropanoate obtained by Example 149-1 and ammonium acetate in a manner similar to that of Example 64-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.72(6H, s), 2.48(1H, br-s), 3.84(3H, s), 3.96(3H, s), 6.77(1H, d, J=8.4Hz), 6.92(2H, d, J=8.8Hz), 7.48(2H, d, J=8.8Hz), 7.84(1H, dd, J=8.4,2.6Hz), 8.43(1H, d, J=2.6Hz).
MS (ES+) : 341.18 (M+1).

Example 150-1
4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2(3H)-one

A mixture of 2-hydroxy-1,2-bis(4- methoxyphenyl)ethanone (25g) and urethane (24.5g) was heated at 190°C overnight.

The mixture was poured into a mixture of water (150mL) and acetone (150mL). The resulting precipitates were collected, washed with 50% acetone aqueous solution, coevaporated with toluene twice, and triturated with ethyl acetate. The resulting powder was collected, washed with ethyl acetate, and dried in vacuo. This crude product was used for the next step without further purification.

MS (ESI) : 296.2 (M-1).

Example 150-2

4,5-Bis(4-methoxyphenyl)-2-chloro-1,3-oxazole

A mixture of 4,5-bis(4-methoxyphenyl)- 1,3-oxazol-2(3H)-one obtained by Example 150-1 (18.73g), phosphoryl chloride (58.7mL) and triethylamine (8.78mL) was stirred under reflux at 120°C for 5hrs.

The mixture was cooled, concentrated, coevaporated with toluene twice, dissolved in ethyl acetate (150mL), washed with water twice, dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 9/1) to give the crude product, which was purified by recrystallization from methanol (5.5g).

^{1}H NMR ($CDCl_3$) : δ 3.83(3H, s), 3.84(3H, s), 6.80-7.70(8H, m).
MS (ESI) : 338.2 $(M+Na)^+$.

Example 151-1

2-Bromo-1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone

Under a nitrogen atmosphere, pyridinium tribromide (4.62g) was added to a suspension of 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone (3.72g) in a mixture of 30% hydrogen bromide in acetic acid (3mL) and

dichloromethane (30mL).

The mixture was stirred for 30min, and poured into a mixture of cold water and ethyl acetate. The solution was adjusted pH 5 with 10% aqueous potassium dicarbonate and the aqueous layer was separated. The organic layer was washed with 5% aqueous sodium thiosulfate, saturated aqueous sodium hydrogencarbonate and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the title compound (4.88g).

^{1}H-NMR (DMSO-d_6) : δ 3.84 (3H, s), 3.85 (3H, s), 6.83 (1H, d, J = 10.1Hz), 7.08 (2H, d, J = 9Hz), 7.88 (1H, dd, J = 2.6 ,8.6Hz), 8.37 (2H, d, J = 2.4Hz).

Example 151-2

2-Amino-1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride

2-Bromo-1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone obtained by Example 151-1 (1.82g) was dissolved in dimethylformamide (18mL) and the solution was cooled at 0℃. Ammonium gas was bubbled into the solution for 30imn. Ammonium gas was ceased and nitrogen was passed through the solution for 15min at the same temperature.

The solution was poured into a mixture of cold water and ethyl acetate, and the aqueous layer was separated. The organic layer was washed with water and brine, and dried over magnesium sulfate. The solution was conecntrated to about 20mL and 4N hydrochloric acid in ethyl acetate (0.6mL) was added. The resulting precipitate was collected by filtration, washed with ethyl acetate, and dried in vacuo to give the title compound (1.44g).

^{1}H-NMR (DMSO-d_6) : δ 3.85(3H, s), 3.88(3H, s), 6.89(1H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.88(1H, dd, J=2.2, 8.6Hz), 8.03(2H, d, J=8.8Hz), 8.92(1H, d, J=2Hz).

Example 151-3

2-{[2-(4-Methoxyphenyl)-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate

Under a nitrogen atmosphere, acetoxyacetyl chloride (0.75mL) and triethylamine (2.6mL) was added successively to a soluton of 2-amino-1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 151-2 (1.43g) in dichloromethane (15mL) at 0℃.

The mixture was stirred for 2hrs at the same temperature, and poured into a mixture of cold water and ethyl acetate. The aqueous layer was separated And the organic layer was washed with diluted aqueous hydrochloric acid, water and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the title compound (1.51g).

^{1}H-NMR (DMSO-d_6) : δ 2.11(3H, s), 3.81(3H, s), 3.83(3H, s), 4.53(2H, s), 6.8(1H, d, J=8.6Hz), 7.01(2H, d, J=8.8Hz), 7.68(1H, dd, J=2.3, 8.6Hz), 7.96(2H, d, J=8.8Hz), 8.26(1H, d, J=2.3Hz), 8.88(1H, d, J=7Hz).

MS (ESI) : 395.2 $(M+Na)^+$.

Example 151-4

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate

To a mixture of triphenylphosphine (3.17g), iodine (3.07g) and triethylamine (3.4ml) in dichloromethane (30mL), a solution of 2-{[2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate obtained by Example 151-3 (1.5g) in dichloromethane (15mL) was added at 0℃ under nitrogen, and the mixture was stirred overnight at same temperature.

The reaction mixture was poured into cold water and dichloromethane. The organic layer was separated, washed with 1 N aqueous hydrochloric acid, water, saturated sodium bicarbonate

solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (255mg).

^{1}H-NMR (DMSO-d_6) : δ 2.12(3H, s), 3.83(3H, s), 3.87(3H, s), 5.23(2H, s), 6.89(1H, d, J=8.6Hz), 7.05(2H, d, J=8.9Hz), 7.47(2H, d, J=8.9Hz), 7.82(1H, dd, J=2.5 ,8.6Hz), 8.34(1H, d, J=2.5Hz).
MS (ESI) : 377.2 $(M+Na)^+$.

Example 152
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid

1N aqueous sodium hydroxide solution (2.33mL) solution was added to a solution of ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate (100mg) in methanol (0.5mL) and tetrahydrofuran (0.5mL) at 0℃.

After stirring for 10hrs at room temperature, the pH of the solution was justified to 1 with 1N hydrochloric acid. The precipitate was produced, which was collected by filtration to give the title compound (94.0mg).

MS (ESI) : 402 $(M+H)^+$.

Example 153
1-{[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (44.9mg) was added to a solution of 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid obtained bye Example 152 (94.0mg) in dimethylformamide (1.0mL) at room temperature. After stirring for 5min, 1-hydroxybenzotriazole hydrate (HOBT) was added to the mixture

at room temperature. After stirring for 5min, to the mixture was added piperidine. The mixture was stirred for 3days.

The products were extracted with ethyl acetate. The combined extracts were washed with brine, drid over magnesium sulfate, and evaporated. The residue was purified by preparative thin layer chromatography to give the title compound (90.1mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.7(6H, br-s), 3.7-3.78(2H, m), 3.81(3H, s), 4-4.09(2H, m), 5.08(2H, s), 6.92(2H, d, J=8.5Hz), 6.97(2H, d, J=9Hz), 7.29-7.5(5H, m), 7.52-7.66(4H, m).
MS (ESI) : 469 $(M+H)^+$.

Example 154
4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol

The title compound was obtained from 1-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine obtained by Example 153 in a manner similar to Example 163 described later.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.49 (6H, br-s), 3.72-3.87(2H, m), 3.84(3H, s), 4.19-4.35(2H, m), 6.91(2H, d, J=9Hz), 7.01(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.6(2H, d, J= 9Hz).

Example 155
4,5-Bis(4-methoxyphenyl)-2-methoxy-1,3-oxazole

To a solution of 4,5-bis(4-methoxyphenyl)-2-chloro-1,3-oxazole obtained by Example 150-2 (102mg) in methanol (10ml), 28% sodium methoxide in methanol (1ml) was added dropwise, and the mixture was stirred at 60°C for 1hr.

The mixture was concentrated, diluted with water, and extracted with dichloromethane three times. The combined extracts were concentrated. The residue was chromatographed on silica gel

(n-hexane/ethyl acetate = 4/1) to give the title compound (83mg).

^{1}H-NMR ($CDCl_3$) : δ 3.82(3H, s), 3.83(3H, s), 4.14(3H, s), 6.70-7.70(8H, m).

MS (ESI) : 312.2 $(M+H)^+$.

Example 156

7-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine dihydrochloride

A mixture of 4,5-bis(4-methoxyphenyl)-2-chloro-1,3-oxazole obtained by Example 150-2 (100mg), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine dihydrochloride (92.2mg), potassium carbonate (438mg) in dimethylsulfoxied (10ml) was stirred at 120°C overnight.

The mixture was cooled, diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. The residue was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as an eluent to give the title compound, which was converted to the corresponding hydrochloride salt (47mg).

^{1}H-NMR (DMSO-d_6) : δ 2.00-5.00(19H, m), 6.80-7.70(8H, m).

MS (ESI) : 403.3 $(M+H)^+$ (free).

Example 157

4,5-Bis(4-methoxyphenyl)-2-(methylthio)-1,3-oxazole

A mixture of 4,5-bis(4-methoxyphenyl)-2-chloro-1,3-oxazole obtained by Example 150-2 (3g) and sodium thiomethoxide (1.33g) in ethanol was stirred at 85°C for 1.2hrs.

The mixture was cooled, diluted with ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated to give the title compound (3.12g).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.83(6H, s), 6.80-7.80(8H, m).
MS (ESI) : 328.1 $(M+H)^+$.

Example 158

4,5-Bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole

A mixture of 4,5-bis(4-methoxyphenyl)-2-(methylthio)-1,3-oxazole obtained by Example 157 (3.07g), m-chloroperbenzoic acid (4.85g) in dichloromethane was stirred at room temperature overnight.

The mixture was concentrated, diluted with ethyl acetate, washed with sodium thiosulfate ($Na_2S_2O_3$) aqueous solution, sodium hydrogencarbonate aqueous solution and brine. The combined extracts were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (dichloromethane) to afford a solid, which was triturated with diisopyopylether to give the titele compound (1.9g).

^{1}H-NMR ($CDCl_3$) : δ 3.41(3H, s), 3.85(3H, s), 3.86(3H, s), 6.80-7.80(8H, m).
MS (ESI) : 382.1 $(M+Na)^+$.

Example 159

N-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]-N,N',N'-trimethyl-1,2-ethanediamine dihydrochloride

A mixture of 4,5-bis(4-methoxyphenyl)-2-chloro-1,3-oxazole obtained by Example 150-2 (200mg) and N,N,N'-trimethyl-1,2-ethanediamine (324mg) in dioxane was stirred at 85℃ overnight.

The mixture was cooled, diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. The residue was purified by thin layer chromatography (dichloromethane/methanol = 9/1) to give the title compound, which was converted to the corresponding dihydrochloride (192mg).

^{1}H-NMR (DMSO-d_6) : δ 2.00-5.00(19H, m), 6.80-7.70(8H, m).
MS (ESI) : 382.3 $(M+H)^+$ (free).

Example 160-1

Ethyl {[1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate

Ethyl chlorooxoacetate (427 mg) was added to a solution of 2-amino-2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)ethanone hydrochloride (1.00g) in benzene (20mL) at room temperature. The mixture was refluxed for 1hr.

The products were extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrrogencarbonate aquetous solution and brine, dried over magnesium sulfate, and evaporated in vacuo to afford the title compound (1.20g).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.37(3H, t, J=7Hz), 3.83(3H, s), 4.34(2H, q, J=7Hz), 4.99(2H, s), 6.42(1H, d, J=7.5Hz), 6.87(2H, d, J=6Hz), 6.91(2H, d, J=6Hz), 7.27-7.45(6H, m), 7.95(2H, d, J=9Hz), 8.49(1H, d, J=7.5Hz).
MS (ESI) : 470 $(M+Na)^+$.

Example 160-2

Ethyl 4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate

Phosphorus oxychloride (1.00mL) was added to a solution of ethyl {[1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 160-1 (1.20g) in toluene (12mL) at 0℃. The mixture was refluxed for 15hrs.

The products were extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium

sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (752 mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.45(3H, t, J=7.1Hz), 3.84(3H, s), 4.51(2H, q, J=7.1Hz), 5.1(2H, s), 6.91(2H, d, J=8.5Hz), 6.99(2H, d, J=8.5Hz), 7.3-7.5(5H, m), 7.57-7.63(4H, m).
MS (ESI) : 452 $(M+N)^+$.

Example 161
4-[4-(Benzyloxy)phenyl]-N-methoxy-5-(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide

Under a nitrogen atmosphere, trimethylaluminium (0.98M in hexane, 2.48mL) was added to a solution of N,O-dimethylhydroxylamine hydrochloride (504mg) in tetrahydrofuran (10mL) at 0℃. After stirring for 1hr at room temperature, a solution of ethyl 4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 160-2 (740mg) in tetrahydrofuran (14mL) was added to the reaction mixture.

After stirring for 12hrs at 43℃, the reaction mixture was stopped by adding 1N hydrochloric acid at 0℃. The products were extracted with ethyl acetate. The combined extracts were washed with saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (625mg).

^{1}H-NMR (200MHz) : δ 3.33(3H, s), 3.81(3H, s), 3.87(3H, s), 5.14(2H, s), 7.05(2H, d, J=6.5Hz), 7.1(2H, d, J=6.4Hz), 7.32 - 7.57 (9H, m)
MS (ESI) : 467 $(M+Na)^+$.

Example 162
1-[4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

Under a nitrogen atmosphere, isopropylmagnesium chloride (2.0M in diethyl ether, 0.77mL) was added to a solution of 4-[4-(benzyloxy)phenyl]-N-methoxy-5-(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 161 (320mg) in diethyl ether (6.5mL) at -78℃, and the mixture was stirred at 0℃ for 1.5hrs.

The mixture was poured into saturated ammonium chloride aqueous solution and the products were extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (195mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.3(6H, d, J=7Hz), 3.69-3.84(1H, m), 3.85(3H, s), 5.11(2H, s), 6.91(2H, d, J=8.5Hz), 7.01(2H, d, J=8.5Hz), 7.3-7.51(5H, m), 7.59(2H, d, J=6Hz), 7.63(2H, d, J=6Hz).

Example 163

1-[4-(4-Hydroxyphenyl)-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

10% Pd/C (44 mg) was added to 1-[4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone obtained by Example 162 (181mg) in methanol (2.1mL) and dioxane (2.1mL) at room temperature.

After stirring for 10hrs under a hydrogen atmosphere, the mixture was filtered through celite pad and the filtrate was evaporated in vacuo to give the title compound (163mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.3(6H, d, J=7Hz), 3.74-3.85(1H, m), 3.85(3H, s), 5.21(1H, br-s), 6.86(2H, d, J=6.5Hz), 6.91(2H, d, J=6.5Hz), 7.54(2H, d, J=8.5Hz), 7.62(2H, d, J=9Hz).
MS (ESI) : 360 $(M+Na)^+$.

Example 164

1-[4-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-5-(4-m

ethoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

NaH (60% in mineral oil, 14.8mg)was added to a solution of 1-[4-(4-hydroxyphenyl)-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone obtained by Example 163 (160mg) in dimethylformamide (2.3mL) at 0°C. After stirring for 10min, a solution of (2-bromoethoxy)(tert-butyl)dimethylsilane (139mg) in dimethylformamide (2.0mL) was added. The mixture was stirred for 4hrs at room temperature.

The mixture was poured into ice-cooling water and the products were extracted with ethyl acetate. The combined extracts were washed with brine, drid over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography to give the title compound (105mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 0.12(6H, s), 0.92(9H, s), 1.3(6H, d, J=7Hz), 3.74-3.86(1H, m), 3.85(3H, s), 3.93-4.10(m, 4H), 6.9(2H, d, J=8.5Hz), 6.94(2H, d, J=9.0Hz), 7.58(2H, d, J=8.5Hz), 7.62(2H, d, J=9Hz).
MS (ESI) : 496 $(M+H)^+$.

Example 165
5-[4-(Benzyloxy)phenyl]-N-methoxy-4-(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide

The title compound was obtained from ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate in a manner similar to Example 161.

^{1}H-NMR (200MHz, DMSO-d_6) : δ 3.34(3H, s), 3.8(3H, s), 3.87(3H, s), 5.16(2H, s), 7.01(2H, d, J=8.7Hz), 7.14(2H, d, J=8.8Hz), 7.31-7.56(9H, m).
MS (ESI) : 445 $(M+H)^+$.

Example 166
1-[4-[4-(2-Hydroxyethoxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-

2-yl]-2-methyl-1-propanone

Tetrabutylammonium fluoride (1N in tetrahydrofuran 0.424mL) was added to a solution of 1-[4-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone obtained by Example 164 (105mg) in tetrahydrofuran (1.2mL) at 0℃.

After stirring for 1hr, the products were extracted with ethyl acetate. The combined extracts were washed with brine, drid over magnesium sulfate, and evaporated. The residue was purified by preparative thin layer chromatography to give the title compound (36.5mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.3(6H, d, J=3.5Hz), 3.75-3.84(1H, m), 3.85(3H, s), 4(2H, d, J=2.2Hz), 6.91(2H, d, J=4.4Hz), 7.6(2H, d, J=3.3Hz), 7.62(2H, d, J=3.3Hz).
MS (ESI) : 382 $(M+H)^+$.

Example 167-1

2-[4-(Benzyloxy)phenyl]-2-hydroxy-1-(4-methoxyphenyl)ethanone

A mixture of 2-[4-(benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone (2.83g) in acetone (30mL) and water (15mL) was stirred under reflux at 70℃ for 1hr.

The mixture was concentrated, diluted with water, and extracted with ethyl acetate twice. The combined extracts were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 4/1) to give the title compound (1.98g).

^{1}H-NMR ($CDCl_3$) : δ 3.83(3H, s), 4.58(1H, d, J=6.0Hz), 5.01(2H, s), 5.85(1H, d, J=6.0Hz), 6.70-8.10(13H, m).
MS (ESI) : 371.2 $(M+Na)^+$.

Example 167-2

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2(3H)-one

To a warmed (80 ℃) solution of 2-[4-(benzyloxy)phenyl]-2-hydroxy-1-(4-methoxyphenyl)ethanone obtained by Example 167-1 (4.1g) in dimethylformamide (8mL) were added potassium cyanate (1.91g) and acetic acid (1.48mL) in sequence.

After stirring at this temperature under a nitrogen atmosphere for 2hrs, the mixture was poured into water (30mL). The resulting powder was collected, washed with water, coevaporated with toluene, and dried in vacuo to give the crude product (4.87g), which was used for the next step without further purification.

MS (ESI) : 372.3 $(M-1)^-$.

Example 167-3
5-[4-(Benzyloxy)phenyl]-2-chloro-4-(4-methoxyphenyl)-1,3-oxazole

The title compound was obtained from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2(3H)-one obtained by Example 167-2 in a manner similar to Example 150-2.

^{1}H-NMR ($CDCl_3$) : δ 3.84(3H, s), 5.09(2H, s), 6.80 - 7.80(13H, m).
MS (ESI) : 392.2 $(M+H)^+$.

Example 168
5-[4-(Benzyloxy)phenyl]-2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol e

To a suspension of 5-[4-(benzyloxy)phenyl]-2-chloro-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 167-3 (1g) in methanol (20mL) was added dropwise 28% methanol solution of sodium methoxide (5.2mL).

After stirring at 60℃ overnight, the mixture was concentrated, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over magnesium sulfate and concentrated. The

residue was triturated with methanol, and the resulting powder was collected, washed with methanol, and dried in vacuo (50℃) to give the title compound (0.72g).

^{1}H-NMR ($CDCl_3$) : δ 3.82(3H, s), 4.14(3H, s), 5.07(2H, s), 6.70-7.70(13H, m).
MS (ESI) : 388.3 $(M+H)^+$.

Example 169

5-(4-Hydroxyphenyl)-2-methoxy-4-(4-methoxyphenyl)-1,3-oxazole

A mixture of 5-[4-(benzyloxy)phenyl]-2-methoxy-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 168 (0.72g) and 20% palladium hydroxide (dry base) on carbon (wet; 0.22g) in ethanol (10mL) and cyclohexene (5mL) was stirred under reflux at 95℃ for 2hrs.

The mixture was filtered and concentrated to give the title compound (490mg).

^{1}H-NMR ($CDCl_3$) : δ 3.83(3H, s), 4.14(3H, s), 5.11(1H, s), 6.70-7.70(8H, m).
MS (ESI) : 298.1 $(M+H)^+$.

Example 170

2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

A mixture of 5-(4-hydroxyphenyl)-2-methoxy-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 169 (486mg), (2-bromoethoxy)(tert-butyl)dimethylsilane (1.17 g), potassium carbonate (1.13g) and potassium iodide (814mg) in dimethylformamide was stirred at 75℃ for 3hrs.

The mixture was diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. To a solution of the residue in tetrahydrofuran was added 1M

tetrahydrofuran solution of tetrabutylammoniumfluoride (7mL), and the mixture was stirred at room temperature under a nitrogen atmosphere for 1.5hrs.

The reaction mixture was quenched with water and extracted with ethyl acetate twice. The combined extracts were washed with water twice and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 1/1) to give the title compound (346mg).

^{1}H-NMR ($CDCl_3$) : δ 2.01(1H, t, J=6.0Hz), 3.82(3H, s), 3.85-4.30(7H, m), 6.70-7.70(8H, m).
MS (ESI) : 364.1 $(M+Na)^+$.

Example 171

2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

To a solution of 2-{4-[2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 170 (334mg) and triethylamine (0.409mL) in ethyl acetate, methanesulfonylchloride (0.114 ml) was added dropwsie. And the mixture was stirred at room temperature for 1hr.

The reaction mixture was quenched with water and extracted with ethyl acetate twice. The combined extracts were dried over magnesium sulfate and concentrated to give the crude procuct (0.44g), which was used for the next step without further purification.

Example 172

2-(2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

A mixture of crude 2-{4-[2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 171 (0.44g) and potassium phthalimide (272mg) in dimethylformamide was stirred at 60 ℃

overnight.

The mixture was cooled, diluted with water, and extracted with ethyl acetate twice. The conbined extracts were dried over magnesium sulfate and concentrated to give the crude product (0.57g), which, was used for the next step without further pirification.

MS (ESI) : 493.1 $(M+Na)^+$.

Example 173

(2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine

A mixture of the crude 2-(2-{4-[2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 172 (0.57g) and hydrazine monohydrate (0.142 ml) in ethanol was stirred at 70°C for 2hrs.

The mixture was cooled, diluted with water, extracted with dichloromethane three times. The combined extracts were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (dichloromethane/methanol = 9/1) to give the title compound (246mg) as an oil.

^{1}H-NMR ($CDCl_3$) : δ 1.00-4.30(12H, m), 6.60-7.70(8H, m).
MS (ESI) : 341.2 $(M+H)^+$.

Example 174

N-(2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

A mixture of (2-{4-[2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine obtained by Example 173 (80mg), trimethylsilylisocyanate (0.16mL) and triethylamine (0.16mL) in dichloromethane was stirred at room temperature overnight.

The reaction mixture was quenched with water and extracted with

ethyl acetate twice. The combined extracts were washed with water three times, dried over magnesium sulfate, and concentrated. The residue was purified by preparative thin-layer chromatography (dichloromethane/methanol = 9/1) to give the title compound (54mg).

^{1}H-NMR ($CDCl_3$) : δ 2.80-5.60(13H, m), 6.40-8.30(8H, m).
MS (ESI) : 441.20 $(M+Na)^+$.

Example 175

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole

1N NaOH aqueous solution (51.7mL) was added to a solution of ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate (1.11g) in methanol (9.0mL) and tetrahydrofuran (25.0mL) at 0°C.

After stirring for 1hr at room temperature, the pH of the mixture was justified to 1 with 1N hydrochloric acid followed by extraction with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (800mg).

^{1}H-NMR (200MHz, DMSO-d_6) : δ 3.78(3H, s), 5.14(2H, s), 6.98(2H, d, J=4.4Hz), 7.11(2H, d, J=4.4Hz), 7.32-7.52(9H, m), 8.43(1H, s).
MS (ESI) : 358 $(M+H)^+$.

Example 176

4-[4-(4-Methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound was obtained from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 175 in a manner similar to Example 163.

Example 177

5-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-meth

oxyphenyl)-1,3-oxazole

The title compound was obtained from 4-[4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 176 and (2-bromoethoxy)(tert-butyl)dimethylsilane in a manner similar to Example 164.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 0.01(6H, s), 0.81(9H, s), 3.73(3H, s), 3.9-3.99(4H, m), 6.8(4H, d, J=8.8Hz), 7.41(2H, d, J=8.9Hz), 7.47(2H, d, J=8.9Hz), 7.79(1H, s).
MS (ESI) : 426 $(M+H)^+$.

Example 178
2-{4-[4-(4-Methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound was obtained from 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 177 in a manner similar to Example 166.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.12(1H, br-s), 3.81(3H, s), 3.97-4.02(2H, m), 4.1-4.14(2H, m), 6.86-6.97(4H, m), 7.53(2H, d, J=9Hz), 7.58(2H, d, J=9Hz), 7.9(1H, s).
MS (ESI) : 312 $(M+H)^+$.

Example 179
5-[5-[4-(Benzyloxy)phenyl]-2-(1-piperidinylcarbonyl)-1,3-oxazol-4-yl]-2-methoxypyridine

To a solution of N,O-dimethylhydroxyamine hydrochloride (509 mg) in dry benzene (4.2mL), 2.3mL of triethylaluminum (2M solution in toluene) was added dropwise at 0℃ under nitrogen atmosphere. And the mixture was stirred at room temperature for 2hrs. A solution of ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-

carboxylate (720mg) in dry benzene (16.7mL) was added dropwise to the mixture at room temperature and the reaction mixture was refluxed for 2hrs.

The reaction mixture was cooled to room temperature and quenched with 5% aqueous hydrochloric acid. The mixture was poured into 1M aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica-gel eluting with n-hexane and ethyl acetate to give the title compound (550mg).

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.75(6H, br-s), 3.6-3.7(2H, m), 3.89(3H, s), 3.9-4.0(2H, m), 5.16(2H, s), 6.91(1H, d, J=9.0Hz), 7.14(2H, d, J=8.9Hz), 7.3-7.6(7H, m), 7.86(1H, dd, J=9.0,2.3Hz), 8.37(1H, d, J=2.3Hz).
MS (ESI) : 492.2 $(M+Na)^+$.

Example 180
4-[4-(6-Methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol

10% Palladium on carbon (50% wet, 50mg) and ammonium formate (210mg) was added to a solution of 5-[5-[4-(benzyloxy)phenyl]-2-(1-piperidinylcarbonyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 179 (520mg) in ehtanol(10mL), tetrahydrofuran (4mL) and water (3mL). The mixture was stirred at reflux condition for 4hrs and cooled to room temperature.

After filtration through celite, the filtrate was concentared in vacuo. The residue was dissolved in a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (330mg).

^{1}H-NMR (DMSO-d_6) d : 1.5-1.75(6H, br-s), 3.6-3.7(2H, m), 3.89(3H, s), 3.9-4.0(2H, m), 5.16(2H, s), 6.91(1H, d, J=9.0Hz), 7.14(2H, d, J=8.9Hz), 7.3-7.6(7H, m), 7.86(1H, dd, J=9.0,2.3Hz), 8.37(1H, d, J=2.3Hz).

MS (ESI) : 492.2 $(M+Na)^+$.

Example 181

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethanol

Under a nitrogen atmosphere, sodium hydride(12.7mg) was added to a solution of 4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol obtained by Example 180 (100mg) in dimethylformamide (5mL) at 0 ℃. After 10min, a solution of (2-bromoethoxy)trimethylsilane (104mg) in dimethylformamide (1mL) was added. The whole mixture was stirred overnight at room temperature.

The mixture was poured into a mixture of water and ethyl acetate, and the aqueous layer was separated. The organic layer was washed with water, brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in tetrahydrofuran (5mL). Tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.52mL) was added to this solution.

The mixture was stirred at room temperature for 3hrs, and poured into into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (86mg).

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.8(6H, br-s), 3.55-3.8(4H, m), 3.89(3H, s), 3.85-3.95(2H, m), 4.05(2H, t), 4.92(1H, t, J=5.5Hz), 6.91(1H,

d, J=8.6Hz), 7.07(2H, d, J=8.7Hz), 7.51(2H, d, J=8.7Hz), 7.85(1H, dd, J=8.6,2.3Hz), 8.38(1H, J=2.3Hz).
MS (ESI) : 466.0 $(M+CH_3CN)^+$.

Example 182
tert-Butyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

Under a nitrogen atmosphere, sodium hydride(59mg) was added to a solution of 4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol obtained by Example 180 (280mg) in dimethylformamide (5mL) at 0 ℃. After 10min, a solution of tert-butyl (2-bromoethyl)carbamate (496mg) in dimethylformamide (1mL) was added. The whole mixture was stirred overnight at room temperature.

The mixture was poured into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (361mg).

^{1}H-NMR (DMSO-d_6) : δ 1.38(9H, s), 1.6-1.8(6H, br-s), 3.25-3.4(4H, m), 3.6-3.7(2H, b), 3.88(3H, s), 3.8-4.1(4H, m), 6.91(1H, d, J=8.7Hz), 7.05(2H, d, J=8.8Hz), 7.51(2H, d, J=8.8Hz), 7.86(1H, dd, J=8.7,2.2Hz), 8.38(1H, J=2.2).
MS (ESI) : 545.0 $(M+Na)^+$.

Example 183
5-[4-(Benzyloxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide

The title compound (480mg) was obtained from ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate (680mg) and N,O-dimethylhydroxylamine hydrochloride

(385mg) in a manner similar to Example 179.

^{1}H-NMR (DMSO-d_6) : δ 3.87(3H, s), 3.89(6H, s), 5.16(2H, s), 6.92(1H, d, J=8.5Hz), 7.15(2H, d, J=8.8Hz), 7.4-7.6(7H, m), 7.88(1H, dd, J=8.5,2.3Hz), 8.40(1H, d, J=2.3Hz).
MS (ESI) : 468.0 $(M+Na)^+$.

Example 184

4,5-Bis(4-methoxyphenyl)-2-[(1-methyl-3-pyrrolidinyl)oxy]-1,3-oxazole

To a suspension of sodium hydride (40mg, 60% in mineral oil) and 1-methyl-3-pyrrolidinol (101mg), 4,5-bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole obtained by Example 158 (120mg) was added in portions. And the mixture was stirred at room temperature overnight.

The mixture was diluted with water and extracted with ethyl acetate twice. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by thin layer chromatography (dichloromethane/methanol = 9/1) to give the title compound as an oil (121mg)

^{1}H-NMR ($CDCl_3$) : δ 0.70-3.10(9H, m), 3.82(3H, s), 3.83(3H, s), 5.41(1H, m). 6.80-7.70(8H, m).
MS (ESI) : 403.13 $(M+Na)^+$.

Example 185

4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenol

To a solution of 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazole (0.88g) in chloroform was added dropwise trimethylsilyliodide (1.45mL) at 0℃, and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with methanol (1mL), stirred for 15 min, diluted with water, and extracted with ethyl

acetate.

The organic phase was washed with water, 10% sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 7/3) to give the title compound (0.63 g).

^{1}H NMR ($CDCl_3$) : δ 2.71(3H, s), 3.83(3H, s), 5.28(2H, s), 6.70-7.70(8H, m).

Mass (ESI) : 314.2 $(M+H)^+$.

Example 186

2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethanol

A mixture of 4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenol obtained by Example 185 (0.63g), (2-bromoethoxy)(tert-butyl)dimethylsilane (721mg), potassium carbonate (1.39g) and potassium iodide (1g) in dimethylformamide was stirred at 75°C for 2hrs.

The mixture was diluted with water, and extracted with ethyl acetate twice. The combined extracts were washed with water three times, dried over magnesium sulfate, and concentrated.

To a solution of the residue in tetrahydrofuran, 1M tetrahydrofuran solution of tetrabutylammonium fluoride (6mL) was added dropwise at 0°C, and the mixture was stirred at room temperature for 30min. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water twice and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 1/1) to give the title compound (0.71g).

^{1}H-NMR ($CDCl_3$) : δ 2.03(1H, t, J=6.2Hz), 2.71(3H, s), 3.83(3H, s), 3.90-4.20(4H, m), 6.70-7.70(8H, m).

MS (ESI) : 358.20 $(M+H)^+$.

Example 187

2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound was obtained from 2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 186 in a manner similar to Example 171.

Example 188

2-(2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound was obtained from 2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 187 in a manner similar to Example 172.

^{1}H-NMR ($CDCl_3$) : δ 2.70(3H, s), 3.82(3H, s), 4.00-4.30(4H, m), 6.70-8.00(12H, m).
MS (ESI) : 509.27 $(M+Na)^+$.

Example 189

(2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine

The title compound was obtained from 2-(2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 188 in a manner similar to Example 173.

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.11(2H, m), 3.83(3H, s), 4.02(2H, t, J=5.1Hz), 6.70-7.80(8H, m).
MS (ESI) : 357.20 $(M+H)^+$.

Example 190

N-(2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was obtained from (2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine obtained by Example 189 in a manner similar to Example 221 described later.

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.03(3H, s), 3.56(2H, m), 3.84(3H, s), 4.13(2H, t, J=5.0Hz), 4.76(1H, br-s), 6.80-7.80(8H, m).
MS (ESI) : 457.27 $(M+Na)^+$.

Example 191

N-(2-{4-[4-(4-Methoxyphenyl)-2-(methylsulfinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide obtained by Example 190 in a manner similar to Example 193 described later.

^{1}H-NMR ($CDCl_3$) : δ 3.04(3H, s), 3.19(3H, s), 3.58(2H, m), 3.85(3H, s), 4.15(2H, t, J=5.0Hz), 4.78(1H, br-s), 6.80-7.70(8H, m).
MS (ESI) : 472.87 $(M+Na)^+$.

Example 192

N-(2-{4-[4-(4-Methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

A mixture of N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide obtained by Example 191 (38mg) and m-chloroperbenzoic acid (44 mg) in dichloromethane was stirred at room temperature overnight. The mixture was diluted with AcOEt, washed with 10% NaHSO3 aqueous

solution, saturated NaHCO3 aqueous solution and brine, dried over magnesium sulfate and concentrated to give the title compound (34 mg).

^{1}H-NMR ($CDCl_3$) : δ 3.04(3H, s), 3.41(3H, s), 3.58(2H, m), 3.85(3H, s), 4.13(2H, t, J=5.0Hz), 4.77(1H, t, J=6.0Hz), 6.80-7.80(8H, m).
MS (ESI) : 488.87 $(M+Na)^+$.

Example 193

2-{4-[4-(4-Methoxyphenyl)-2-(methylsulfinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

A mixture of 2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 186 (63mg) and oxone (325mg) in tetrahydrofuran (15mL) and water (15mL) was stirred at room temperature for 2hrs.

The mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was purified by preparative thin-layer chromatography (ethyl acetate) to give the title compound (28mg).

^{1}H-NMR ($CDCl_3$) : δ 2.00(1H, t, J=6.1Hz), 3.18(3H, s), 3.85(3H, s), 3.90-4.20(4H, m), 6.80-7.70(8H, m).
MS (ESI) : 396.20 $(M+H)^+$.

Example 194

tert-Butyl (2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

A mixture of 4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenol obtained by Example 185 (186mg), tert-butyl (2-bromoethyl)carbamate (399mg), potassium carbonate (410mg) and potassium iodide (493mg) in dimethylformamide was stirred at 80°C for 2hrs.

The reaction mixture was cooled, dilute with water, and extracted

with ethyl acetate twice. The combined extracts were washed with water three times, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 4/1) to give the title compound (252mg).

^{1}H-NMR ($CDCl_3$) : δ 1.00-5.40(19H, m), 6.60-7.70(8H, m).
MS (ESI) : 479.1 $(M+Na)^+$.

Example 195
(2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride

To a solution of tert-butyl (2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 194 (249mg) in ethyl acetate (5mL) was added 4N hydrogen chloride in ethyl acetate (5mL), and the mixture was stirred at room temperature for 3hrs.

The resulting powder was collected, washed with ethyl acetate, and dried in vacuo to give the title compound (194mg).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.22(2H, m), 3.78(3H, s), 4.22(2H, t, J=5.0Hz), 6.80-7.70(8H, m), 8.23(3H, br-s).
MS (ESI) : 357.1 $(M+H)^+$ (free).

Example 196
N-(2-{4-[4-(4-Methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

To a mixture of (2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride obtained by Example 195 (191mg) and sodium acetate (80mg) in dimethylformamide (3mL) and water (2mL) was added potassium cyanate (79mg), and the mixture was stirred at room temperature overnight.

The mixture was diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. The

residue was chromatographed on silica gel (dichloromethane/methanol = 9/1) to give the title compound (126mg).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.62(2H, m), 3.82(3H, s), 4.06(2H, t, J=5.0Hz), 4.51(2H, br-s), 5.03(1H, br-s), 6.70-7.60(8H, m).
MS (ESI) : 422.2 $(M+Na)^+$.

Example 197
N-(2-{4-[4-(4-Methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

A mixture of N-(2-{4-[4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 196 (123mg) and m-chloroperbenzoic acid (213mg) in dichloromethane was stirred at room temperature overnight.

The mixture was diluted with ethyl acetate, washed with 10% sodium hydrogencarbonate aqueous solution, saturated hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and concentrated. The residue was triturated with ethanol, and the resulting powder was collected, washed with ethanol, and dried in vacuo to give the title compound (90mg).

^{1}H-NMR ($CDCl_3$) : δ 3.41(3H, s), 3.63(2H, m), 3.85(3H, s), 4.09(2H, t, J=5.0Hz), 4.37(2H, br-s), 4.90(1H, br-s), 6.80-7.80(8H, m).
MS (ESI) : 454.1 $(M+Na)^+$.

Example 198
(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride

4N hydrogen chloride solution in ethyl acetate (0.67 mL) was added to a solution of tert-butyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 182 (350mg) in ethyl acetate (5mL) at 0°C. The mixture was stirred overnight at

room temperature.

The product was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (259mg).

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.8(6H, m), 3.1-3.3(2H, m), 3.6-3.7(2H, m), 3.89(3H, s), 3.8-4.0(2H, m), 4.26(2H, t, J=4.9Hz), 6.93(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.56(2H, d, J=8.9Hz), 7.85(1H, dd, J=8.6,1.9Hz), 8.2-8.3(2H, br-s), 8.37(1H, d, J=1.9Hz).
MS (ESI) : 423.0 $(M+H)^+$.

Example 199
N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

Under a nitrogen atmosphere, methanesulfonyl chloride (42.7mg) was added to a solution of (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride obtained by Example 198 (114mg) and triethylamine (101mg) in dichloromethane (1.5mL) at 0℃.

The mixture was poured into a mixture of cold water and ethyl acetate, and stirred for 20min. The aqueous layer was separated and the organic layer was washed with diluted hydrochloric acid, water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (60mg).

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.7(6H, m), 2.96(3H, s), 3.3-3.4(2H, m), 3.6-3.7(2H, m), 3.89(3H, s), 3.9-4.0(2H, m), 4.0-4.1(2H, m), 6.92(1H, d, J=8.6Hz), 7.08(2H, d, J=8.7Hz), 7.53(2H, d, J=8.7Hz), 7.86(1H, dd, J=8.6,2.2Hz), 8.37(1H, d, J=2.2Hz).
MS (ESI) : 522.9 $(M+Na)^+$.

Example 200

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

A solution of potassium cyanate (49.1mg) in water (1mL) was added to a mixture of (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride obtained by Example 198 (139mg) and sodium acetate (49.7mg) in a mixture of dimethylformamide (2mL) and water (0.5mL) at room temperature.

The mixture was stirred overnight at 50℃, and was poured into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (77mg).

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.8(6H, m), 3.3-3.4(2H, m), 3.6-3.7(2H, m), 3.89(3H, s), 3.8-4.1(4H, m), 5.55(2H, s), 6.19(1H, t, J=5.6Hz), 6.91(1H, d, J=8.6Hz), 7.07(2H, d, J=8.7Hz), 7.53(2H, d, J=8.7Hz), 7.86(1H, dd, J=8.6,2.2Hz), 8.38(1H, d, J=2.2Hz).
MS (ESI) : 488.0 $(M+Na)^+$.

Example 201

[5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol

Under a nitrogen atmoshere, potassium carbonate (383mg) was added to a solution of [5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate (995mg) in methanol (20mL) at room tempetarue.

The mixture was stirred overnight at the same temperature and poured into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent,

the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (790mg).

^{1}H-NMR (DMSO-d_6) : δ 3.87(3H, s), 4.58(2H, d, J=6.2Hz), 2.57(1H, t, J=-515.2Hz), 6.88(1H, d, J=8.6Hz), 7.12(2H, d, J=8.8Hz), 7.3-7.6(7H, m), 7.82(1H, dd, J=2.4,8.6Hz), 8.35(1H, d, J=2.3Hz).
MS (ESI) : 389.0 $(M+H)^+$.

Example 202
1-[5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

Under a nitrogen atmosphere, isobutylmagnesium bromide (2M solution in tetrahydrofuran, 1.5mL) was added to a solution of 5-[4-(benzyloxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 183 (632mg) in tetrahydrofuran (10mL) at -78℃. The mixture was warmed to 0℃ and stirred for 3hrs at the same temperature.

The reaction mixture was quenched with saturated aqueous ammonium chloride, and the mixture was poured into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (361mg).

^{1}H-NMR (DMSO-d_6) : δ 0.97(6H, d, J=6.6Hz), 2.1-2.3(1H, m), 2.97(2H, d, J=6.9Hz), 3.90(3H, s), 5.16(2H, s), 6.93(1H, d, J=8.6Hz), 7.15(2H, d, J=8.9Hz), 7.3-7.6(7H, m), 7.88(1H, dd, J=8.6,1.8Hz), 8.37(1H, d, J=1.8Hz).
MS (ESI) : 465.0 $(M+Na)^+$.

Example 203
[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl](cy

clopropyl)methanone

The title compound was obtained from 5-[4-(benzyloxy)phenyl]-N-methoxy-4-(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 165 in a manner similar to Example 162.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.05-1.2(2H, m), 1.28-1.4(2H, m), 3.07-3.26(1H, m), 3.85(3H, s), 5.1(2H, s), 6.94(2H, d, J=6.5Hz), 6.98(2H, d, J=6.4Hz), 7.3-7.5(5H, m), 7.55-7.67(4H, m).
MS (ESI) : 426 $(M+H)^+$.

Example 204
4-[2-(1-Hydroxybutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound was obtained from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl](cyclopropyl)methanone obtained by Example 203 in a manner similar to Example 163.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 0.97(3H, t, J=7.3Hz), 1.34-1.64 (2H, m), 1.8-2.08(2H, m), 2.94(1H, br-s), 3.82(3H, s), 4.85(1H, t, J=6.5Hz), 5.86(1H, br-s), 6.81(2H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.43(2H, d, J=8.5Hz), 7.54(2H, d, J=8.5Hz).
MS (ESI) : 340 $(M+H)^+$.

Example 205
1-[5-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-1-butanol

The title compound was obtained from 4-[2-(1-hydroxybutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 204 in a manner similar to Example 164.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 0.11(5H, s), 0.91(9H, s), 0.98(3H, t,

J=7.3Hz), 1.37-1.64(2H, m), 1.84-2.07(2H, m), 3.02(1H, br-s), 3.83(3H, s), 3.91-4.08(4H, m), 4.84(1H, t, J=6.5Hz), 6.89(2H, d, J=8Hz), 6.89(2H, d, J = 8Hz), 7.48(2H, d, J = 8Hz), 7.55(2H, d, J= 8Hz).

MS (ESI) : 498 $(M+H)^+$.

Example 206

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-1-butanol

The title compound was obtained from 1-[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-1-butanol obtained by Example 205 in a manner similar to Example 166.

^{1}H-NMR (200MHz) : δ 0.98(3H, t, J=7.3Hz), 1.36-1.7(2H, m), 1.76-2.12(2H, m), 3.83(3H, s), 3.93-4.04(2H, m), 4.05-4.15(2H, m), 4.85(1H, t, J=6.5Hz), 6.9(4H, d, J=8Hz), 7.5(2H, d, J=9.5Hz), 7.55(2H, d, J=9.5Hz).

MS (ESI) : 384 $(M+H)^+$.

Example 207

1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

The title compound was obtained from 5-[4-(benzyloxy)phenyl]-N-methoxy-4-(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 165 in a manner similar to Example 162.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.01(3H, s), 1.05(3H, s), 2.26-2.5(1H, m), 3(2H, d, J=7Hz), 3.85(3H, s), 5.1(2H, s), 6.94(2H, d, J=7.5Hz), 6.98(2H, d, J=7.5Hz), 7.36-7.48(5H, m), 7.58(2H, d, J=6Hz), 7.63(2H, d, J=6Hz).

Example 208

1-[5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

The title compound was obtained from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone obtained by Example 207 in a manner similar to Example 163.

Example 209

tert-Butyl (2-{4-[4-(4-methoxyphenyl)-2-(3-methylbutanoyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

The title compound was obtained from 1-[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone obtained by Example 208 in a manner similar to Example 215 described later.

Example 210

1-[5-[4-(2-Aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone hydrochloride

The title compound was obtained from tert-butyl (2-{4-[4-(4-methoxyphenyl)-2-(3-methylbutanoyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 209 in a manner similar to Example 216 described later.

Example 211

N-(2-{4-[4-(4-Methoxyphenyl)-2-(3-methylbutanoyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from 1-[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone hydrochloride obtained by Example 210 in a manner similar to Example 217 described later.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.01(3H, s), 1.05(3H, s), 2.25-2.51(1H, m), 3(2H, d, J=7Hz), 3.56-3.7(2H, m), 3.85(3H, s), 4-4.12(2H, m), 4.49(2H, br-s), 5.08(1H, t, J=5.7Hz), 6.88(2H, d, J=9Hz), 6.94(2H, d, J=9Hz), 7.57(2H, d, J=6.5Hz), 7.61(2H, d, J=6.5Hz).
MS (ESI) : 438 $(M+H)^+$, 481 $(M+HCO_2)^-$.

Example 212
N-(2-{4-[4-(4-Methoxyphenyl)-2-(3-methylbutanoyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was obtained from 1-[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone hydrochloride obtained by Example 210 in a manner similar to Example 218 described later.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.01(3H, s), 1.05(3H, s), 2.28-2.48(1H, m), 2.99(2H, s), 3.03(3H, s), 3.5-3.64(2H, m), 3.85(3H, s), 4.14(2H, t, J=5Hz), 4.92(1H, t, J=6Hz), 6.88(2H, d, J=9Hz), 6.94(2H, d, J=9Hz), 7.57(2H, d, J=9Hz), 7.62(2H, d, J=9Hz).
MS (ESI) : 473 $(M+H)^+$, 516 $(M+HCO_2)^-$.

Example 213
1-[5-(4-Hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-3-methyl-1-butaone

The title compound (190mg) was obtained from 1-[5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone obtained by Example 202 (340mg) in a manner similar to Example 180.

^{1}H-NMR (DMSO-d_6) : δ 1.5-1.8(6H, br-s), 3.6-3.7(2H, m), 3.8-3.9(2H, m), 3.88(3H, s), 6.8-6.95(3H, m), 7.40(2H, d, J=8.6Hz), 7.85(1H, dd, J=8.7,2.4Hz), 8.37(1H, d, J=2.4Hz).
MS (ESI) : 353.0 $(M+H)^+$.

Example 214

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

The title compound (55mg) was obtained from 1-[5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-3-methyl-1-butaone obtained by Example 213 (120mg) in a manner similar to Example 181.

^{1}H-NMR (DMSO-d_6) : δ 0.96(6H, d, J=6.8Hz), 2.1-2.3(1H, m), 2.97(1H, d, J=6.9Hz), 3.6-3.8(2H, m), 3.90(3H, s), 4.0-4.1(2H, m), 4.92(1H, t, J=5.5Hz), 6.9-7.2(3H, m), 7.55(2H, d, J=8.7Hz), 7.87(1H, dd, J=8.5,2.4Hz), 8.38(1H, d, J=2.4Hz).

MS (ESI) : 419.2 $(M+Na)^+$.

Example 215

tert-Butyl (2-{4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

NaH (60% in mineral oil, 64.1 mg) was added to a solution of 4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol obtained by Example 154 (303mg) in dimethylformamide (2.0mL) at 0℃. After stirring for 15 min, a solution of tert-butyl (2-bromoethyl)carbamate (449 mg) in dimethylformamide (2.0mL) was added. The mixture was stirred for 10hrs at 45℃.

The mixture was poured into saturated ammonium chloride aqueous solution at 0℃ and the products were extracted with ethyl acetate. The combined extracts were washed with brine, drid over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography to give the title compound (485mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.46(9H, s), 1.71(6H, br-s), 3.43-3.63(2H, m), 3.68-3.81(2H, m), 3.85(3H, s), 4-4.15(4H, m), 5(1H, br-s),

6.88(2H, d, J=6.5Hz), 6.92(2H, d, J=6.5Hz), 7.56(2H, d, J=3Hz), 7.61(2H, d, J=3Hz).

MS (ESI) : 521 $(M+H)^+$.

Example 216

(2-{4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride

4N HCl-dioxane (2.50 mL) was added to a solution of tert-butyl (2-{4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 215 (485mg) in dichloromethane (2.5mL) at 0℃.

After stirring for 2hrs at room temperature, the mixture was evaporated in vacuo to give the title compound (616mg).

MS (LC) : 422 $(M+H)^+$ (free).

Example 217

N-(2-{4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

Triethylamine (141mg) and trimethylsilyl isocyanate (80.4mg) were added to a solution of (2-{4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride obtained by Example 216 (213mg) in dichlorimethane (2.2mL) at 0℃.

After stirring for 10hrs at room temperature, the product was extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated under reduced presure. The residue was triturated in isopropylether to give the title compound (92.0mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.71(6H, br-s), 3.56-3.66(2H, m), 3.71-3.78(2H, m), 3.84(3H, s), 4.05(2H, t, J=2.5Hz), 4.08-4.17(2H,

m), 4.55(2H, br-s), 5.11-5.23(1H, m), 6.86(2H, d, J=4.4Hz), 6.91(2H, d, J=4.4Hz), 7.5-7.63(4H, m).
MS (ESI) : 465$(M+H)^+$.

Example 218
N-(2-{4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

Triethylamine (141mg) and methanesulfonyl chloride (79.9mg) were added to a solution of (2-{4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride obtained by Example 216 (213mg) in dichloromethane (2.2mL) at 0℃.

After stirring for 10hrs at room temperature, the product was extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated under reduced presure. The residue was purified by preparative thin layer chromatography to give the title compound (114mg).

^{1}H-NMR (200MHz) : δ 1.71(6H, br-s), 3.02(3H, s), 3.43-3.8(4H, m), 3.84(3H, s), 4-4.14(4H, m), 5.15(1H, t, J=5.9Hz), 6.86(2H, d, J=8.9Hz), 6.92(2H, d, J=8.9Hz), 7.53-7.6(4H, m).
MS (ESI) : 500 $(M+H)^+$.

Example 219
N-(2-{4-[4-(4-Methoxyphenyl)-2-(2,2,2-trifluoroethoxy)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

To a solution of 2,2,2-trifluoroethanol (102mg) and sodium hydride (60% in mineral oil; 41mg) in dioxane, N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 (88mg) was added. And the mixture was stirred at room temperature overnight under a nitrogen atmosphere.

The reaction mixture was quenched with water, extracted with dichloromethane three times. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by preparative thin-layer chromatography (dichloromethane/methanol = 9/1) to give the title compound (70mg).

^{1}H NMR ($CDCl_3$) : δ 3.61(2H, m), 3.83(3H, s), 4.07(2H, t, J=4.9Hz), 4.39(1H, br-s), 4.84(2H, q, J=8.0Hz), 4.94(1H, br-s), 6.80-7.70(8H, m).
MS (ESI) : 474.1 $(M+Na)^+$.

Example 220
N-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-pyridinamine

A mixture of 4,5-bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole obtained by Example 158 (132mg), 2-aminopyridine (104mg) and sodium hydride (60% in mineral oil; 44mg) in dioxane was stirred at 85°C under a nitrogen atmosphere for 3hrs.

The reaction mixture was cooled, quenched with water, and extracted with ethyl acetate twice. The combined extracts were washed with water three times, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (n-hexane/ethyl acetate = 1/1) to give the title compound (34mg).

^{1}H-NMR ($CDCl_3$) : δ 3.85(3H, s), 3.86(3H, s), 6.70-8.40(13H, m).
MS (ESI) : 374.2 $(M+H)^+$.

Example 221
N-(2-{4-[2-Methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

To a solution of (2-{4-[2-methoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amine obtained by Example 173 (73mg) and triethylamine (90μL) in dichloromethane, methanesulfonylchloride (25μL) was added dropwsie.

And the mixture was stirred at room temperature for 2hrs. The reaction mixture was quenched with water and extracted with ethyl acetate twice. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by preparative thin-layer chromatography (dichloromethane/methanol = 9/1) to give the title compound (47mg).

^{1}H-NMR ($CDCl_3$) : δ 2.90-5.00(14H, m), 6.60-7.70(8H, m).
MS (ESI) : 441.20 $(M+Na)^+$.

Example 222
N-(2-{4-[2-Ethoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 1.48(3H, t, J=7.1Hz), 3.50-4.20(7H, m), 4.40(2H, br-s), 4.53(2H, q, J=7.1Hz), 5.01(1H, br-s), 6.70 - 7.70(8H, m).
MS (ESI) : 398.2 $(M+H)^+$.

Example 223
N-(2-{4-[2-Isopropoxy-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 1.47(2H, d, J=6.1Hz), 3.60(2H, m), 3.83(3H, s), 4.05(2H, t, J=4.9Hz), 4.40(2H, br-s), 4.95(1H, br-s), 5.17(1H, heptet, J=6.1Hz), 6.70-7.70(8H, m).

MS (ESI) : 434.2 $(M+Na)^+$.

Example 224

N-(2-{4-[2-(Isopropylthio)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 1.49(6H, d, J=6.9Hz), 3.60-4.20(8H, m), 4.42(2H, br-s), 4.96(1H, br-s), 6.70-7.70(8H, m).
MS (ESI) : 428.2 $(M+H)^+$.

Example 225

N-(2-{4-[2-(Isopropylsulfonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[2-(isopropylthio)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 224 in a manner similar to Example 197.

^{1}H-NMR ($CDCl_3$) : δ 1.50(6H, d, J=6.9Hz), 3.40-3.70(3H, m), 3.85(3H, s), 4.09(2H, t, J=5.0Hz), 4.45(2H, br-s), 5.00(1H, br-s), 6.80-7.80(8H, m).
MS (ESI) : 482.0 $(M+Na)^+$.

Example 226

N-(2-{4-[2-(2-Ethoxyethoxy)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]

phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 3.40-4.20(11H, m), 4.44(2H, br-s), 4.61(2H, m), 4.99(1H, br-s), 6.70-7.70(8H, m).
MS (ESI) : 442.3 $(M+H)^+$.

Example 227
2-(Isopropylthio)-4,5-bis(4-methoxyphenyl)-1,3-oxazole

To a solution of 2-propanethiol (127mg) and sodium hydride (60% in mineral oil; 67mg) in dioxane, 4,5-bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole obtained by Example 158 (120 mg) was added. And the mixture was stirred at room temperature overnight under a nitrogen atmosphere.

The reaction mixture was quenched with water, and extracted with dichloromethane twice. The combined extracts were dried over magnesium sulfate and concentrated to give the title compound (134mg).

^{1}H-NMR ($CDCl_3$) : δ 1.49(6H, d, J=6.9Hz), 3.70-4.00(7H, m), 6.70-7.80(8H, m).
MS (ESI) : 356.2 $(M+H)^+$.

Example 228
N-(2-{4-[2-(Dimethylamino)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

A mixture of N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 (100mg) in 50% dimethylamine aqueous solution (5mL) and dioxane (5mL) was stirred at 60°C for 3hrs.

The mixture was diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. The residue was triturated with ethanol, the resulting powder was

collected, washed with ethanol, and dried in vacuo to give the title compound (46mg).

^{1}H-NMR ($CDCl_3$) : δ 3.12(6H, s), 3.60(2H, m), 3.83(3H, s), 4.04(2H, t, J=5.0Hz), 4.40(2H, br-s), 4.96(1H, br-s), 6.70-7.70(8H, m).
MS (ESI) : 397.1 $(M+H)^+$.

Example 229
N-(2-{4-[2-(Cyclopentyloxy)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 0.80-4.20(15H, m), 4.43(2H, br-s), 4.98(1H, br-s), 5.38(1H, m), 6.70-7.70(8H, m).
MS (ESI) : 460.2 $(M+Na)^+$.

Example 230
N-(2-{4-[2-(2-Fluoroethoxy)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 3.50(2H, m), 3.83(3H, s), 4.06(2H, t, J=4.9Hz), 4.45(2H, br-s), 4.60-5.00(4H, m), 5.00(1H, br-s), 6.70-7.70(8H, m).
MS (ESI) : 416.4 $(M+H)^+$.

Example 231
N-(2-{4-[2-(2,2-Difluoroethoxy)-4-(4-methoxyphenyl)-1,3-oxazol-5

-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl] phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 3.40-6.60(13H, m), 6.70-7.70(8H, m).
MS (ESI) : 456.2 $(M+Na)^+$.

Example 232-1
(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)acetic acid

2-Benzofuran-1,3-dione was added to a solution of aminoacetic acid (10.0g) in dioxane (40mL) at room temperature. The mixture was refluxed for 2hrs.

The mixture was evaporated under reduced presure. The residue was triturated in water to give the title compound (28.5g).

^{1}H-NMR (200MHz, DMSO-d_6) : δ 3.42(1H, br-s), 4.33(2H, s), 7.81-8.02(4H, m).

Example 232-2
1-[4-(Benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetate

(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)acetic acid obtained by Example 232-1 (670mg) and cesium carbonate (1.06g) were added to a solution of 2-[4-(benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone (1.28g) in acetone(13.0mL) at 0℃.

After stirring for 10hrs at room temperature, the mixture was evaporated under reduced presure. The residue was triturated in isopropylether to give the title compound (566mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.8(3H, s), 4.51(1H, d, J=17.4Hz), 4.72(1H, d, J=17.5Hz), 5.03(2H, s), 6.75-6.98(5H, m), 7.33-7.42(7H, m), 7.66-7.79(2H, m), 7.81-7.95(4H, m).

MS (ESI) : 558 $(M+Na)^+$.

Example 232-3

2-{[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-1H-isoindole-1,3(2H)-dione

Ammonium acetate (432mg) was added to a solution of 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetate obtained by Example 232-2 (300mg) in acetic acid (5.60mL) at room temperature.

The mixture was refluxed for 1.5hrs, and evaporated under reduced presure. The residue was washed with saturated sodium hydrogencarbonate aqueous solution and water to give the title compound (181mg).

^{1}H-NMR (200MHz, DMSO-d_6) : δ 3.76(3H, s), 5(2H, s), 5.13(2H, s), 6.94(2H, d, J=8.9Hz), 7.08(2H, d, J=8.9Hz), 7.36-7.57(9H, m), 7.78-8.03(4H, m).

Example 233

1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanamine

Hydrazine monohydrate (4.47g) was added to 2-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-1H-isoindole-1,3(2H)-dione obtained by Example 232-3 (5.77g) in tetrahydrofuran (58.0mL) at room temperature.

After a stirring for 1hr at 80°C, the mixture was washed with 0.1N hydrochloric acid and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give the title compound (5.29g).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.83(3H, s), 4.01(2H, s), 5.08(2H, s),

6.9(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.3-7.59(9H, m).
MS (ESI) : 387 $(M+H)^+$.

Example 234

5-[4-(Benzyloxy)phenyl]-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

The title compound (900mg) was obtained from ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate (1.0g) in a manner similar to Example 179.

^{1}H-NMR (DMSO-d_6) : δ 1.17(3H, t, J=7Hz), 1.27(3H, t, J=6.9Hz), 3.48(2H, q, J=7.1Hz), 3.76(2H, q, J=6.9Hz), 3.89(3H, s), 5.16(2H, s), 6.92(1H, d, J=9.1Hz), 7.15(2H, d, J=8.9Hz), 7.3-7.6(7H, m), 7.86(1H, dd, J=2.4,8.7Hz), 8.4(1H, d, J=2.4Hz).
MS (ESI) : 458.2 $(M+H)^+$.

Example 235

N,N-Diethyl-5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

20% Palladium hydroxide on carbon (50% wet, 272mg) was added to a solution of 5-[4-(benzyloxy)phenyl]-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 234 (890mg) in ethanol (15mL) and cyclohexene (5mL). The mixture was stirred at reflux condition for 10 hour and cooled to room temperature.

After filtration through celite, the reaction mixture was evaporated. The residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (621mg).

^{1}H-NMR (DMSO-d_6) : δ 1.16(3H, t, J=7Hz), 1.27(3H, t, J=6.9Hz), 3.34(2H, br-s), 3.47(2H, q, J=7Hz), 3.77(2H, q, J=7Hz), 3.88(3H, s), 6.8-7(3H, m), 7.41(2H, d, J=9.5Hz), 7.85(1H, dd, J=2.4,8.7Hz).

MS (ESI) : 390.2 $(M+Na)^+$.

Example 236

N,N-Diethyl-5-[4-(2-hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

The title compound (135mg) was obtained from N,N-diethyl-5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 235 (200mg) in a manner similar to Example 181.

^{1}H-NMR (DMSO-d_6) : δ 1.17(3H, t, J=7Hz), 1.28(3H, t, J=6.9Hz), 3.48(2H, q, J=7Hz), 3.7-3.8(4H, m), 3.89(3H, s), 4.05(2H, t, J=4.8Hz), 4.92(1H, t, J=5.5Hz), 6.92(1H, d, J=8.7Hz), 7.07(2H, d, J=8.8Hz), 7.53(2H, d, J=8.8Hz), 7.86(1H, dd, J=2.4,8.6Hz), 8.4(1H, d, J=2.2Hz).
MS (ESI) : 434.2 $(M+Na)^+$.

Example 237

N-(2-{4-[2-(Ethylthio)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 1.50(3H, t, J=7.4Hz), 3.24(2H, q, J=7.4Hz), 3.50-4.20(7H, m), 4.40(2H, br-s), 4.97(1H, br-s), 6.70-7.70(8H, m).
MS (ESI) : 436.3 $(M+Na)^+$.

Example 238

N-(2-{4-[2-(Ethylsulfonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from

N-(2-{4-[2-(ethylthio)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 237 in a manner similar to Example 197.

^{1}H-NMR ($CDCl_3$) : δ 1.50(3H, t, J=7.4Hz), 3.50(2H, q, J=7.4Hz), 3.60-4.20(7H, m), 4.46(2H, br-s), 4.98(1H, br-s), 6.80-7.80(8H, m).
MS (ESI) : 468.2 $(M+Na)^+$.

Example 239

N-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]acetamide

A mixture of 4,5-bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole obtained by Example 158 (150mg),acetamide (123mg) and sodium hydride (60% in mineral oil; 84mg) in dioxane was stirred at 70°C for 3hrs.

The mixture was diluted with ethyl acetate, washed with water three times, dried over magnesium sulfate, and concentrated. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 1/1) to give the title compound (91mg).

^{1}H-NMR ($CDCl_3$) : δ 1.58(3H, s), 3.82(3H, s), 3.83(3H, s), 6.70-7.70(8H, m).
MS (ESI) : 339.2 $(M+H)^+$.

Example 240

2-{[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]thio}ethanol

The title compound was obtained from 4,5-bis(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazole obtained by Example 158 in a manner similar to Example 227.

^{1}H-NMR ($CDCl_3$) : δ 3.30-4.20(10H, m), 6.80-7.70(8H, m).
MS (ESI) : 380.3 $(M+Na)^+$.

Example 241

N-(2-{4-[2-{[2-(Dimethylamino)ethyl]thio}-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 197 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 2.32(6H, s), 2.74(2H, t, J=7.0Hz), 3.78(2H, t, J=7.0Hz), 3.50-4.20(7H, m), 4.46(2H, br-s), 5.03(1H, br-s), 6.70-7.80 (8H, m).
MS (ESI) : 457.3 $(M+H)^+$.

Example 242
tert-Butyl (2-{4-[2-[(diethylamino)carbonyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

The title compound (601mg) was obtained from N,N-diethyl-5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 235 (444mg) in a manner similar to Example 182.

^{1}H-NMR (DMSO-d_6) : δ 1.17(3H, t, J=7Hz), 1.28(3H, t, J=6.9Hz), 1.38(9H, s), 3.2-3.3(2H, m), 3.48(2H, q, J=7Hz), 3.77(2H, q, J=6.9Hz), 3.89(3H, s), 4.02(2H, t, J=5.6Hz), 6.92(1H, d, J=8.5Hz), 7.06(2H, d, J=8.8Hz), 7.52(2H, d, J=8.8Hz), 7.86(1H, dd, J=2.4,8.6Hz), 8.4(1H, d, J=1.9Hz).
MS (ESI) : 511.3 $(M+H)^+$.

Example 243
5-[4-(2-Aminoethoxy)phenyl]-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide hydrochloride

The title compound (430mg) was obtained from tert-butyl N,N-diethyl-5-(4-hydroxyphenyl)-4-(6-

methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 242 (580mg) in a manner similar to Example 198.

^{1}H-NMR (DMSO-d_6) : δ 1.16(3H, t, J=7.0Hz), 1.27(3H, t, J=7.0Hz), 3.1-3.3(2H, m), 3.48(2H, q, J=7.0Hz), 3.77(2H, q, J=7.0Hz), 3.89(3H, s), 4.27(2H, t, J=4.9Hz), 6.93(2H, d, J=8.5Hz), 7.12(2H, d, J=8.8Hz), 7.57(2H, d, J=8.8Hz), 7.86(1H, dd, J=8.5,1.9Hz), 8.36(2H, br-s), 8.39(1H, dd, J=1.9Hz).

Example 244

N,N-Diethyl-4-(6-methoxy-3-pyridinyl)-5-(4-{2-[(methylsulfonyl)amino]ethoxy}phenyl)-1,3-oxazole-2-carboxamide

The title compound (144mg) was obtained from 5-[4-(2-aminoethoxy)phenyl]-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide hydrochloride obtained by Example 243 (200mg) in a manner similar to Example 199.

^{1}H-NMR (DMSO-d_6) : δ 1.17(3H, t, J=6.9Hz), 1.28(3H, t, J=6.9Hz), 2.97(3H, s), 3.3-3.5(4H, m), 3.77(2H, q, J=6.9Hz), 3.89(3H, s), 4.10(2H, t, J=5.4Hz), 6.92(1H, d, J=8.6Hz), 7.09(2H, d, J=8.7Hz), 7.33(1H, t, J=5.8Hz), 7.54(2H, d, J=8.7Hz), 7.86(1H, dd, J=8.6,2.1Hz), 8.39(1H, d, J=2.1Hz).
MS (ESI) : 489.2 $(M+H)^+$.

Example 245

4-Nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

Under a nitrogen atmosphere, 4-nitrophenyl chloroformate (202mg) was added to a suspension of (2-{4-[4-(6-methoxy-3-pyridinyl)-2-trifluoromethyl-1,3-oxazol-5-yl]phenoxy}ethyl)amine hydrochloride (416mg) and triethylamine (253mg) in dichloromethane (10ml) at 0°C.

The mixture was stirred at the same temperature for 2hrs, and

poured into a mixture of cold water and ethyl acetate. The mixture was adjusted pH 1 with 1N aqueous hydrochloric acid and the aquesous layer was separeated. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the title compound (511mg).

^{1}H-NMR (DMSO-d_6) : δ 3.3-3.6(2H, m), 3.89(3H, s), 4.1-4.3(2H, m), 6.93(1H, d, J=9.0Hz), 7.12(2H, d, J=8.8Hz), 7.57(2H, d, J=8.8Hz), 7.86(1H, dd, J=9.0,1.8Hz), 8.1-8.4(5H, m).

Example 246

N-(2-Hydroxyethyl)-N'-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

Under a nitrogen atmopshere, hydroxyethylamine (44.9mg) was added to a solution of 4-nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 245 (200mg) in dimethylformamide (5mL) at 0°C. Ice bath was removed after 5min and the mixture was stirred at room temperature for 2hrs.

The mixture was poured into a mixture of cold water and ethyl acetate. The aquesous layer was separeated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to afford the title compound (90.1mg).

^{1}H-NMR (DMSO-d_6) : δ 3.67(2H, q, J=5.5Hz), 3.3-3.5(4H, m), 3.89(3H, s), 4.02(2H, t, J=5.5Hz), 6.05(1H, t, J=5.6Hz), 6.24(1H, t, J=5.6Hz), 6.93(1H, d, J=8.6Hz), 7.10(2H, d, J=8.8Hz), 7.55(2H, d, J=8.8Hz), 7.86(1H, dd, J=8.6,2.3Hz), 8.37(1H, d, J=2.3Hz).
MS (ESI) : 488.9 $(M+Na)^+$.

Example 247

5-(4-{2-[(Aminocarbonyl)amino]ethoxy}phenyl)-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

The title compound (120mg) was obtained from 5-[4-(2-aminoethoxy)phenyl]-N,N-diethyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide hydrochloride obtained by Example 243 (203mg) in a manner similar to Example 200.

^{1}H-NMR (DMSO-d_6) : δ 1.20(3H, t, J=7.9Hz), 1.31(3H, t, J=7.9Hz), 3.3-3.6(4H, m), 3.77(2H, q, J=7.9Hz), 3.89(3H, s), 4.02(2H, t, J=5.4Hz), 5.58(2H, s), 6.22(1H, t, J=5.6Hz), 6.91(1H, d, J=8.6Hz), 7.08(2H, d, J=8.7Hz), 7.53(2H, d, J=8.7Hz), 7.86(1H, dd, J=8.6,2.2Hz), 8.39(1H, d, J=2.2Hz).
MS (ESI) : 476.2 $(M+Na)^+$.

Example 248
2-({[(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)amino]carbonyl}amino)acetamide

The title compound (108mg) was obtained from 4-nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 245 (200mg) and glycinamide hydrochloride (81.2mg) in a manner similar to Example 246.

^{1}H-NMR (DMSO-d_6) : δ 3.3-3.5(2H, m), 3.61(2H, d, J=5.4Hz), 3.89(3H, s), 4.02(2H, t, J=5.4Hz), 6.18(1H, t, J=5.4Hz), 6.44(1H, t, J=5.4Hz), 6.93(1H, d, J=8.7Hz), 6.98(1H, br-s), 7.10(2H, d, J=8.8Hz), 7.29(1H, br-s), 7.55(2H, d, J=8.8Hz), 7.86(1H, dd, J=8.7,2.2Hz), 8.37(1H, d, J=2.2Hz).
MS (ESI) : 502.1 $(M+Na)^+$.

Example 249
N-(2-Methoxyethyl)-N'-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (112mg) was obtained from 4-nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 245 (150mg) and 2-methoxyethylamine (62.1mg) in a manner similar to Example 246.

^{1}H-NMR (DMSO-d_6) : δ 3.1-3.6(6H, m), 3.24(3H, s), 3.89(3H, s), 4-4.1(2H, m), 6.06(1H, br-s), 6.2(1H, br-s), 6.93(1H, d, J=8.6Hz), 7.1(2H, d, J=8.4Hz), 7.55(2H, d, J=8.4Hz), 7.86(1H, d, J=8.6,2.3Hz), 8.38(1H, d, J=2.3Hz).
MS (ESI) : 503.2 $(M+Na)^+$.

Example 250
N-{[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide

Propanoyl chloride (503mg) and pyridine (1.47mL) was added to a solution of 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanamine obtained by Example 233 (1.40g) in dimethylformamide (14.0mL) at 0℃.

After stirring for 1.5hrs at room temperature, the product was extracted with diethylether, washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography to give the title compound (1.18g).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.21(3H, t, J=7.6Hz), 2.32(2H, q, J=7.5Hz), 3.83(3H, s), 4.63(2H, d, J=5.5Hz), 5.08(2H, s), 6.25(1H, br-s), 6.9(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.32-7.56(9H, m).
MS (ESI) : 443 $(M+H)^+$, 465 $(M+Na)^+$.

Example 251
N-{[5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide

The title compound was obtained from N-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 250 in a manner similar to Example 163.

MS (ESI) : 353 $(M+H)^+$.

Example 252

N'-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanamine obtained by Example 233 and dimethylcarbamic chloride in a manner similar to Example 250.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.95(6H, s), 3.83(3H, s), 4.6(2H, d, J=5.3Hz), 5.08(2H, s), 5.29(1H, br-s), 6.89(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.32-7.6(9H, m).

MS (ESI) : 480 $(M+Na)^+$, 458$(M+H)^+$.

Example 253

N'-{[5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from N'-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 252 in a manner similar to Example 255 described later.

MS (ESI) : 368 $(M+H)^+$.

Example 254

Methyl {[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanamine obtained by Example 233 and methyl chloridocarbonate in a manner similar to Example 250.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.74(3H, s), 3.84(3H, s), 4.57(2H, d, J=5.6Hz), 5.09(2H, s), 5.37(1H, br-s), 6.9(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.33-7.58(9H, m).

MS (ESI) : 467 $(M+Na)^+$.

Example 255

Methyl {[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

Thioanisole (1.06mL) was added to a solution of methyl {[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate obtained by Example 254 (1.00g) in trifluoroacetic acid (10.0mL) at 0℃.

After stirring for 10hrs at room temperature, the mixture was poured into ice-cooling water. The pH of the mixture was justified to 10 with sodium hydroxide followed by extraction with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated in isopropylether to give the title compound (799mg).

MS (ESI) : 353 $(M-H)^-$.

Example 256

N-{[5-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide

The title compound was obtained from N-{[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 251 and

(2-bromoethoxy)(tert-butyl)dimethylsilane in a manner similar to Example 164.

MS (ESI) : 511 $(M+H)^+$.

Example 257

N-{[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide

The title compound was obtained from N-{[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 256 in a manner similar to Example 166.

^{1}HNMR (200MHz, $CDCl_3$) : δ 1.21(3H, t, J=7.5Hz), 2.33(2H, q, J=7.5Hz), 3.84(3H, s), 3.92-4.04(2H, m), 4.05-4.15(2H, m), 4.64(2H, d, J=5Hz), 6.22(1H, br-s), 6.9(4H, d, J=8.5Hz), 7.49(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz).

MS (ESI) : 419 $(M+Na)^+$, 397 $(M+H)^+$.

Example 258

tert-Btyl [2-(4-{4-(4-methoxyphenyl)-2-(propionylamino)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate

The title compound was obtained from N-{[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 251 and tert-butyl (2-bromoethyl)carbamate in a manner similar to Example 215.

MS (ESI) : 496 $(M+H)^+$.

Example 259

Methyl {[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}-ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl }carbamate obtained by Example 255 and (2-bromoethoxy)(tert-butyl)dimethylsilane in a manner similar to Example 164.

MS (ESI) : 513 $(M+H)^+$.

Example 260

Methyl {[5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate obtained by Example 259 in a manner similar to Example 166.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.74(3H, s), 3.83(3H, s), 3.92-4.04(2H, m), 4.09-4.14(2H, m), 4.57(2H, d, J=5.5Hz), 5.4(1H, br-s), 6.9(2H, d, J=8.5Hz), 6.9(2H, d, J=9Hz), 7.49(2H, d, J=8.5Hz), 7.53(2H, d, J=9Hz).

MS (ESI) : 421 $(M+Na)^+$, 399 $(M+H)^+$.

Example 261

Methyl {[5-(4-{2-[(tert-butoxycarbonyl)amino]ethoxy}-phenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl }carbamate obtained by Example 255 and tert-butyl (2-bromoethyl)carbamate in a manner similar to Example 215.

Example 262

N-{[5-[4-(2-Aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2

-yl]methyl}propanamide

4N HCl in dioxane (6.0mL) was added to a solution of tert-butyl [2-(4-{4-(4-methoxyphenyl)-2-[(propionylamino)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate obtained by Example 258 (766mg) in dichloromethane (4.0mL) at 0℃.

After stirring for 1hr at 0℃, the product was washed with saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (336mg).

Example 263

N-{[5-(4-{2-[(Aminocarbonyl)amino]ethoxy}phenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide

Triethylamine (0.182mL) and trimethylsilyl isocyanate (75.2mg) were added to a solution of N-{[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 262 (172mg) in dichloromethane (2.20mL) at 0℃.

After stirring for 10hrs at room temperature, the product was extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated under reduced presure. The residue was triturated in isopropylether, hexane and dichloromethane to give the title compound (62.6mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.21(3H, t, J=7.5Hz), 2.33(2H, q, J=7.7Hz), 3.53-3.68(2H, m), 3.83(3H, s), 4-4.09(2H, m), 4.43(2H, br-s), 4.63(2H, d, J=5Hz), 5.02(1H, br-s), 6.24(1H, br-s), 6.86(2H, d, J=8.5Hz), 6.9(2H, d, J=8.5Hz), 7.47(2H, d, J=9Hz), 7.52(2H, d, J=9Hz).
MS (ESI) : 461 $(M+Na)^+$.

Example 264

N-{[4-(4-Methoxyphenyl)-5-(4-{2-[(methylsulfonyl)amino]ethoxy}ph

enyl)-1,3-oxazol-2-yl]methyl}propanamide

Methanesulfonyl chloride (72.1mg) and triethylamine (0.176mL) were added to a solution of N-{[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}propanamide obtained by Example 262 (166mg) in dichloromethane (2.10mL) at 0℃.

After stirring for 10hrs at room temperature, the product was extracted with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (200mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.21(3H, t, J=7.5Hz), 2.33(2H, q, J=7.5Hz), 3.03(3H, s), 3.51-3.6(2H, m), 3.84(3H, s), 4.1-4.15(2H, m), 4.63(2H, d, J=5Hz), 4.87(1H, br-s), 6.24(1H, br-s), 6.86(2H, d, J=9.5Hz), 6.91(2H, d, J=9.5Hz), 7.49(2H, d, J=6.5Hz), 7.53(2H, d, J=6.5Hz).
MS (ESI) : 496 $(M+Na)^+$.

Example 265
N'-{[5-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from N'-{[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 253 and (2-bromoethoxy)(tert-butyl)dimethylsilane in a manner similar to Example 164.

Example 266
tert-Butyl (2-{4-[2-({[(dimethylamino)carbonyl]-amino}methyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl) carbamate

The title compound was obtained from N'-{[5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 253 and tert-butyl (2-bromoethyl)carbamate in a manner similar to Example 215.

Example 267

N'-{[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from N'-{[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 265 in a manner similar to Example 166.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.16(1H, br-s), 2.97(6H, s), 3.83(3H, s), 3.91-4.04(2H, m), 4.04-4.16(2H, m), 4.61(2H, d, J=5.5Hz), 5.18(1H, br-s), 6.83-6.96(4H, m), 7.49(2H, d, J=9Hz), 7.54(2H, d, J=9Hz). MS (ESI) : 410 $(M-H)^-$.

Example 268-1

5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2(3H)-thione

To a mixture of 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride (2g) and carbon disulfide (CS_2) (870mg) in ethanol, triethylamine (0.91mL) under a nitrogen atmosphere was added dropwise, and the mixture was stirred at room temperature for 1hrs. Triethylamine (0.91mL) was further added, and the mixture was stirred at room temperature for 10min. After water (15mL) was added, the mixture was refluxed at 95℃ for 3hrs.

After the mixture was cooled, the resulting precipitates were removed, and the mother liquor was extracted with dichloromethane twice. The combined extracts were dried over magnesium sulfate and concentrated to give the crude product (2.21g), which was used for

the next step without further purification.

Example 268-2

5-[5-[4-(Benzyloxy)phenyl]-2-(methylthio)-1,3-oxazol-4-yl]-2-methoxypyridine

To a solution of 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2(3H)-thione obtained by Example 268-1 (1.99g) in dimethylformamide (20mL), sodium hydride (60% in mineral oil; 306mg) was added at 0℃ under a nitrogen atmosphere, and the mixture was stirred for 5min. Methyl iodide (0.48mL) was added dropwise, and the mixture was stirred at this temperature for 1.5hrs.

The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water three times, dried over magnesium sulfate, and concentrated. The residue was triturated with methanol, and the resulting powder was collected, washed with methanol, and dried in vacuo to give the title compound (0.99g).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.96(3H, s), 5.09(2H, s), 6.60-8.50(12H, m).
MS (ESI) : 405.00 $(M+H)^+$.

Example 269

4-[4-(6-Methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenol

A mixture of 5-[5-[4-(benzyloxy)phenyl]-2-(methylthio)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 268-2 (0.99g) and thioanisole (1.15mL) in trifluoroacetic acid (10mL) was stirred at room temperature overnight.

The mixture was concentrated, basified with saturated sodium hydrogencarbonate aqueous solution, and extracted with dichloromethane twice. The combined extracts were dried over

magnesium sulfate and concentrated to give the title compound (0.86g).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 4.01(3H, s), 6.70-8.70(8H, m).
MS (ESI) : 315.1 $(M+H)^+$.

Example 270
tert-Butyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate

The title compound was obtained from 4-[4-(6-methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenol obtained by Example 269 in a manner similar to Example 194.

MS (ESI) : 480.2 $(M+Na)^+$.

Example 271
(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine

To a solution of crude tert-butyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 270 (1.38g) in dichloromethane (15mL), trifluoroacetic acid (8mL) was added at 0°C, and the mixture was stirred at this temperature for 1hr.

The mixture was concentrated, basified with 1N sodium hydroxide, and extracted with dichloromethane five times. The combined extracts were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (dichloromethane/methanol = 9/1) to give the title compound (625mg).

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.11(2H, t, J=5.1Hz), 3.96(2H, t, J=5.1Hz), 6.60-8.60(7H, m).
MS (ESI) : 358.1 $(M+H)^+$.

Example 272

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)amine obtained by Example 271 in a manner similar to Example 196.

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.61(2H, m), 4.00(3H, s), 4.06(2H, t, J=4.9Hz), 4.48(2H, br-s), 5.12(1H, br-s), 6.70-8.60(7H, m).
MS (ESI) : 423.1 $(M+Na)^+$.

Example 273
N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(methylthio)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 272 in a manner similar to Example 197.

^{1}H-NMR ($CDCl_3$) : δ 3.42(3H, s), 3.63(2H, m), 3.97(3H, s), 4.09(2H, t, J=5.0Hz), 4.46(2H, br-s), 5.00(1H, br-s), 6.80-8.50(7H, m).
MS (ESI) : 432.45 $(M+Na)^+$.

Example 274
N-(2-{4-[2-(2-Ethoxyethoxy)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was obtained from N-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(methylsulfonyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 273 in a manner similar to Example 219.

^{1}H-NMR ($CDCl_3$) : δ 1.25(3H, t, J=6.9Hz), 3.40-3.90(6H, m), 3.95(3H,

s), 4.06(2H, t, J=4.9Hz), 4.40(2H, br-s), 4.61(2H, m), 4.97(1H, br-s), 6.70-8.70(7H, m).

MS (ESI) : 465.2 $(M+Na)^+$.

Example 275

N'-{[5-[4-(2-Aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from tert-butyl (2-{4-[2-({[(dimethylamino)carbonyl]amino}methyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 266 in a manner similar to Example 262.

Example 276

Methyl {[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-(4-{2-[(tert-butoxycarbonyl)amino]ethoxy}phenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate obtained by Example 261 in a manner similar to Example 262.

Example 277

N-(2-{4-[2-({[(Dimethylamino)carbonyl]amino}methyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was obtained from N'-{[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 275 in a manner similar to Example 264.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.97(6H, s), 3.02(3H, s), 3.48-3.65(2H, m), 3.83(3H, s), 4.07-4.14(2H, m), 4.6(2H, d, J=5.5Hz), 4.97(1H, br-s), 5.23(1H, br-s), 6.85(2H, d, J=9Hz), 6.9(2H, d, J=9Hz), 7.49(2H, d, J=6.5Hz), 7.53(2H, d, J=6.5Hz).

MS (ESI) : 511 $(M+Na)^+$.

Example 278

N'-{[5-(4-{2-[(Aminocarbonyl)amino]ethoxy}phenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea

The title compound was obtained from N'-{[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}-N,N-dimethylurea obtained by Example 275 in a manner similar to Example 263.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.96(6H, s), 3.49-3.7(2H, m), 3.83(3H, s), 3.94-4.09(2H, m), 4.58(2H, d, J=5Hz), 4.65(2H, br-s), 5.27(1H, br-s), 5.43(1H, br-s), 6.82(2H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.43(2H, d, J=9Hz), 7.5(2H, d, J=9Hz).
MS (ESI) : 454 $(M+H)^+$.

Example 279

Methyl {[4-(4-methoxyphenyl)-5-(4-{2-[(methylsulfonyl)amino]ethoxy}phenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate obtained by Example 276 in a manner similar to Example 264.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.03(3H, s), 3.45-3.63(2H, m), 3.74(3H, s), 3.83(3H, s), 4.05-4.18(2H, m), 4.56(2H, d, J=6Hz), 4.85(1H, br-s), 5.43(1H, br-s), 6.86(2H, d, J=6.5Hz), 6.9(2H, d, J=7Hz), 7.49(2H, d, J=6.5Hz), 7.53(2H, d, J=7Hz).
MS (ESI) : 498 $(M+Na)^+$.

Example 280

Methyl {[5-(4-{2-[(aminocarbonyl)amino]ethoxy}-

phenyl)-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate

The title compound was obtained from methyl {[5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl}carbamate obtained by Example 276 in a manner similar to Example 263.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.49-3.68(2H, m), 3.74(3H, s), 3.83(3H, s), 3.95-4.15(2H, m), 4.4-4.7(4H, m), 5.09(1H, br-s), 5.44(1H, br-s), 6.85(2H, d, J=6.5Hz), 6.9(2H, d, J=6.5Hz), 7.47(2H, d, J=9Hz), 7.52(2H, d, J=9Hz).

Example 281

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-2,2-dimethylhydrazinecarboxamide

The title compound (115mg) was obtained from 4-nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 245 (300mg) and N,N-dimethylhydrazine (166mg) in a manner similar to Example 246.

^{1}H-NMR (DMSO-d_6) :d 2.4(6H, s), 3.3-3.5(2H, m), 3.89(3H, s), 4.06(2H, t, J=6Hz), 6.67(1H, t, J=5.9Hz), 6.93(1H, d, J=8.9Hz), 7-7.15(3H, m), 7.54(2H, d, J=8.7Hz), 7.86(1H, dd, J=2.2,8.9Hz), 8.38(1H, d, J=2.2Hz).
MS (ESI) : 488.2 $(M+Na)^+$.

Example 282

5-(4-Hydroxyphenyl)-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide

The title compound (1.29g) was obtained from 5-[4-(benzyloxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide (2.0g) in a manner similar to Example

235.

^{1}H-NMR (DMSO-d_6) : δ 3.34(3H, s), 3.86(3H, s), 3.89(3H, s), 6.88(2H, d, J=8.6Hz), 6.91(1H, d, J=7.3Hz), 7.43(2H, d, J=8.6Hz), 7.87(1H, dd, J=2.5,8.6Hz), 8.4(1H, d, J=2.3Hz).
MS (ESI) : 378.3 $(M+Na)^+$.

Example 283
5-[4-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide

Under a nitrogen atmosphere, sodium hydride(197mg) was added to a solution of 5-(4-hydroxyphenyl)-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 282 (1.46g) in dimethylformamide (15mL) at 0℃. After 10min, a solution of (2-bromoethoxy)trimethylsilane (104mg) in dimethylformamide (1mL) was added. The whole mixture was stirred at room temperature for 30min and at 40℃ for 2hrs.

The mixture was poured into a mixture of cold water and ethyl acetate, and the aqueous layer was separated. The organic layer was washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the title compound (1.38g).

^{1}H-NMR (DMSO-d_6) : δ 0.04(6H, s), 0.86(9H, s), 3.33(3H, s), 3.87(3H, s), 3.89(3H, s), 3.8-3.9(2H, m), 4-4.1(2H, m), 6.91(1H, d, J=9.1Hz), 7.07(2H, d, J=8.9Hz), 7.53(2H, d, J=8.8Hz), 7.87(1H, dd, J=2.4,8.7Hz), 8.4(1H, d, J=2.3Hz).
MS (ESI) : 536.2 $(M+Na)^+$.

Example 284
Cyclopropyl[5-[4-(2-hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanone

Under a nitrogen atmosphere, 0.5M solution of

cyclopropylmagnesium bromide in tetrahydrofuran (1.5mL) was added to a solution of 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 283 (400mg) in tetrahydrofuran (4.2mL) at -78°C.

The mixture was stirred for 3hrs at the same temperature and the reaction mixture was quenched with saturated ammonium chloride aqueous solution. The mixture was poured into a mixture of water and ethyl acetate, and the aqueous layer was separated. The organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in tetrahydrofuran (5mL).

1M solution of tetrabutylammonium fluoride (0.41mL) was added to the solution. The mixture was stirred at room temperature for 1hr, and poured into into a mixture of water and ethyl acetate. The aqueous layer was separated, and the organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (98mg).

^{1}H-NMR (DMSO-d_6) : δ 1.1-1.3(4H, m), 3.0-3.1(1H, m), 3.7-3.8(2H, m), 3.90(3H, s), 4.0-4.1(2H, m), 4.90(1H, t, J=5.5Hz), 6.94(1H, d, J=8.6Hz), 7.07(2H, d, J=8.8Hz), 7.55(2H, d, J=8.8Hz), 7.89(1H, dd, J=8.6,2.3Hz), 8.40(1H, d, J=2.3Hz).
MS (ESI) : 403.1 (M+Na)+.

Example 285
[5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate

Under a nitrogen atmosphere, methanesulfonyl chloride (0.21mL) was added to a solution of [5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol obtained by Example 201 (700mg) and triethylamine

(0.75mL) in dichloromethane (14mL) at -10°C.

The mixture was stirred for 1hr at the same temperature, and poured into a mixture of cold water and ethyl acetate. The aqueous layer was separated, and the organic layer was washed with diluted hydrochloric acid, water and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded the title compound (720mg).

^{1}H-NMR (DMSO-d_6) : δ 3.36(3H, s), 3.88(3H, s), 4.98(2H, s), 5.15(2H, s), 6.9(1H, d, J=8.5Hz), 7.14(1H, d, J=10Hz), 7.3-7.5(7H, m), 7.84(1H, dd, J=2.4,8.7Hz), 8.37(1H, d, J=1.9Hz).

Example 286

5-{5-[4-(Benzyloxy)phenyl]-2-[(4-pyridinylthio)methyl]-1,3-oxazol-4-yl}-2-methoxypyridine

Under a nitrogen atmosphere, 4-mercaptopyridine (250mg) and N,N-diisoproylethylamine (0.39mL) was added successively to a solution of [5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate obtained by Example 285 (700mg) in dimethylformamide (7mL) at 0°C. The mixture was stirred at the same temperature for 2hrs, and poured into a mixture of cold water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to afford the title compound (670mg).

^{1}H-NMR (DMSO-d_6) : δ 3.87(3H, s), 4.67(2H, s), 5.14(2H, s), 6.88(1H, d, J=8.5Hz), 7.1(2H, d, J=8.9Hz), 7.36-7.49(9H, m), 7.79(1H, dd, J=2.5,8.6Hz), 8.32(1H, d, J=2.3Hz), 8.44(2H, dd, J=1.6,4.6Hz).
MS (ESI) : 482.2 $(M+H)^+$.

Example 287

4-{4-(6-Methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxa

zol-5-yl}phenol

Under a nitrogen atmosphere, thioanisole was added to a solution of 5-{5-[4-(benzyloxy)phenyl]-2-[(4-pyridinylthio)methyl]-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 286 (660mg) in trifluoroacetic acid (7mL) at 0℃.

After 30min, ice bath was removed and the mixture was stirred overnight at room temperature. The mixture was poured into a mixture of cold saturated sodium hydrogencarbonate aqueous solution and ethyl acetate. The aqueous layer was separated, the organic layer was washed with saturated sodium hydrogencarbonate aqueous solution, water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to afford the title compound (420mg).

^{1}H-NMR (DMSO-d_6) : δ 3.87(3H, s), 4.66(2H, s), 6.8(2H, d, J=4.7Hz), 6.87(1H, d, J=8.4Hz), 7.29(2H, dd, J=1.9,6.8Hz), 7.48(1H, dd, J=1.6,4.6Hz), 7.78(1H, dd, J=2.5,8.6Hz), 8.32(1H, d, J=2.4Hz), 8.44(2H, dd, J=1.5,4.6Hz), 9.93(1H, s).

Example 288

5-{5-[4-(Benzyloxy)phenyl]-2-[(2-pyridinylthio)methyl]-1,3-oxazol-4-yl}-2-methoxypyridine

The title compound (580mg) was obtained from [5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate obtained by Example 285 (660mg) and 2-mercaptopyridine (236mg) in a manner similar to Example 286.

^{1}H-NMR (DMSO-d_6) : δ 3.86(3H, s), 4.69(2H, s), 5.13(2H, s), 6.86(1H, d, J=8.6Hz), 7.09(2H, d, J=8.8Hz), 7.15-7.5(9H, m), 7.6-7.85(2H, m), 8.31(1H, d, J=2.3Hz), 8.5(1H, dd, J=2.3,8.6Hz).
MS (ESI) : 504.1 $(M+Na)^+$.

Example 289

(E)-Cyclopropyl[5-[4-(2-hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanone oxime

Hydroxylamine hydrochloride (63.9mg) was added to a solution of cyclopropyl[5-[4-(2-hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanone obtained by Example 284 (70mg) in pyridine (3mL) at room temperature. The mixture was stirred at 80℃ for 8hrs and cooled to room temperature.

The solvent was evaporated, and the residue was dissolved in a mixture of water and ethyl acetate. The aqueous layer was separated, and the organic layer was washed with diluted aqueous hydrochloric acid, water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by preparative thin layer chromatography on silica-gel eluting with dichloromethane and acetone to afford the title compound (41mg).

^{1}H-NMR (DMSO-d_6) : δ 0.8-1.0(2H, m), 1.4-2.5(2H, m), 2.4-2.5(1H, m), 3.65-3.75(2H, m), 3.88(3H, s), 4.0-4.1(2H, m), 4.90(1H, t, J=5.5Hz), 6.90(1H, d, J=8.6Hz), 7.04(2H, d, J=8.8Hz), 7.46(2H, d, J=8.8Hz), 7.83(1H, dd, J=8.6,2.3Hz), 8.35(1H, d, J=8.6Hz), 12.03(1H, s).
MS (ESI) : 394.1 $(M-H)^-$.

Example 290-1

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2(3H)-thione

Triethylamine (5.60mL) and carbon disulfide (1.64mL) was added to a solution of 2-amino-1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride (4.00g) in ethanol (40.0mL) at 0℃.

After stirring for 1.5hrs at 55℃, the mixture was poured into ice cooling water at room temperature. The product was extracted with ethyl acetate. The combined extracts were washed with brine ,

dried over magnesium sulfate, and evaporated in vacuo to give the title compound (7.92g).

Example 290-2

2-Methoxy-5-[5-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-4-yl] pyridine

A solution of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2(3H)-thione obtained by Example 290-1 (8.79g) in dimethylformamide (25.0mL) and methyl iodide (3.13mL) in dimethylformamide (23.0mL) was added to a solution of sodium hydride (2.01g) in dimethylformamide (45.0mL) at 0℃.

After stirring for 20min, the reaction mixture was quenched with water at 0℃. The precipitate was produced, which as collected by filtration with isopropylether and it was purified by silica gel column chromatography to give the title compound (4.90g).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.71(3H, s), 3.8(3H, s), 3.94(3H, s), 6.75(1H, d, J=8.5Hz), 6.89(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.82(1H, dd, J=2.5,8.5Hz), 8.43(1H, d, J=2.5Hz).
MS (ESI) : 329 $(M+H)^+$, 351 $(M+Na)^+$.

Example 291

tert-Butyl [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate

The title compound (310mg) was obtained from 4-{4-(6-methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenol obtained by Example 287 (280mg) in a manner similar to Example 182.

^{1}H-NMR (DMSO-d_6) : δ 1.37(9H, s), 3.3-3.4(2H, m), 3.87(3H, s), 3.9-4.0(2H, m), 4.66(2H, s), 6.87(1H, d, J=8.6Hz), 7.01(2H, d, J=8.8Hz), 7.39(2H, d, J=8.8Hz), 7.48(2H, d, J=4.6Hz), 7.78(1H, dd,

J=8.6,2.3Hz), 8.31(1H, d, J=2.3Hz), 8.43(2H, d, J=4.6Hz).
MS (ESI) : 535.2 $(M+H)^+$.

Example 292

[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine

The title compound (218mg) was obtained from tert-butyl [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate obtained by Example 291 (300mg) in a manner similar to Example 198.

^{1}H-NMR (DMSO-d_6) : δ 2.87(2H, t, J=5.6Hz), 3.87(3H, s), 3.95(2H, t, J=5.6Hz), 4.66(2H, s), 6.87(1H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.29(2H, d, J=8.8Hz), 7.4-7.5(4H, m), 7.79(1H, dd, J=8.6,2.5Hz), 8.31(1H, d, J=2.3Hz), 8.44(2H, d, J=4.9Hz).
MS (ESI) : 435.2 $(M+H)^+$.

Example 293

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]methanesulfonamide

The title compound (69mg) was obtained from [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine obtained by Example 292 (80mg) in a manner similar to Example 199.

^{1}H-NMR (DMSO-d_6) : δ 2.96(3H, s), 3.3-3.47(2H, m), 3.87(3H, s), 3.9-4.0(2H, m), 4.67(2H, s), 6.88(1H, d, J=8.6Hz), 7.04(2H, d, J=8.8Hz), 7.3-7.5(5H, m), 7.79(1H, dd, J=8.6,2.3Hz), 8.33(1H, d, J=2.3Hz), 8.44(1H, d, J=4.9Hz).
MS (ESI) : 513.1 $(M+H)^+$.

Example 294

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1

,3-oxazol-5-yl}phenoxy)ethyl]urea

The title compound (104mg) was obtained from [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine obtained by Example 292 (140mg) in a manner similar to Example 200.

^{1}H-NMR (DMSO-d_6) : δ 3.3-3.4(2H, m), 3.87(3H, s), 3.9-4.0(2H, m), 4.67(2H, s), 5.54(2H, s), 6.17(1H, t, J=5.6Hz), 6.87(1H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.40(2H, d, J=8.8Hz), 7.48(2H, d, J=6.2Hz), 7.78(2H, dd, J=8.8,2.4Hz), 8.32(1H, d, J=2.4Hz), 8.44(1H, d, J=3.1Hz).
MS (ESI) : 478.1 $(M+H)^+$.

Example 295

[5-[4-(2-Azidoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](cyclopropyl)methanone

Under a nitrogen atmosphere, methanesulfonyl chloride (90mg) was added to a solution of cyclopropyl[5-[4-(2-hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanone obtained by Example 284 (199mg) and triethylamine (212mg) in dichloromethane (6mL) at -10℃.

The mixture was stirred for 1hr at the same temperature, and poured into a mixture of cold water and ethyl acetate. The aqueous layer was separated, and the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in dimethylformamice (6mL) and sodium azide (68mg) was added to this solution. The mixture was stirred overnight at 50℃, and poured into a mixture of water and ethyl acetate. The aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (223mg).

MS (ESI) : 406.1 $(M+H)^+$.

Example 296

N-(2-{4-[2-(Cyclopropylcarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

Triphenylphosphine (59.5mg) and water (100μL) were added to a solution of [5-[4-(2-azidoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](cyclopropyl)methanone obtained by Example 295 (92mg) in ethyl acetate (2mL). The mixture was stirred overnight at room temperature and dried over magnesium sulfate.

After evaporation of the solvent, the residue was dissolved in dichloromethane (4mL) and cooled at -20°C under a nitrogen atmosphere. Triethylamine (91.8mg) and methanesulfonyl chloride (39mg) were added to this solution.

The mixture was stirred for 45min at the same temperature, and poured into a mixture of cold water and ethyl acetate. The aqueous layer was separated, and the organic layer was washed with diluted hydrochloric acid, water and brine, and dried over magnesium sulfate. After evapoation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to afford the title compound (22.5mg).

^{1}H-NMR (DMSO-d_6) : δ 1.15-1.25(4H, m), 2.95(3H, s), 3.02-3.11(1H, m), 3.32-3.39(2H, m), 3.9(3H, s), 4.1(2H, t, J=5.5Hz), 6.94(1H, d, J=8.5Hz), 7.09(2H, d, J=8.8Hz), 7.31(1H, t, J=5.8Hz), 7.57(2H, d, J=8.8Hz), 7.9(1H, dd, J=2.5,8.6Hz), 8.41(1H, d, J=2.3Hz).
MS (ESI) : 458.0 $(M+H)^+$.

Example 297

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

The title compound (23.0mg) was obtained from

5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 283 (150mg) and isopropylmagnesium bromide (1.29mL) in a manner similar to Example 284.

^{1}H-NMR (DMSO-d_6) : δ 0.9-1.2(1H, m), 1.21(6H, d, J=6.9Hz), 3.5-3.8(2H, m), 3.9(3H, s), 3.95-4.1(2H, m), 4.91(1H, t, J=5.4Hz), 6.94(1H, d, J=8.9Hz), 7.08(2H, d, J=8.8Hz), 7.56(2H, d, J=7Hz), 7.89(1H, dd, J=2.4,8.6Hz), 8.39(1H, d, J=2.4Hz).
MS (ESI) : 405.2 $(M+Na)^+$.

Example 298
N-(2-{4-[2-(Cyclopropylcarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

Triphenylphosphine (76.3mg) and water (100μL) were added to a solution of [5-[4-(2-azidoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](cyclopropyl)methanone obtained by Example 295 (118mg) in ethyl acetate (5mL). The mixture was stirred overnight at room temperature and dried over magnesium sulfate.

After evaporation of the solvent, the residue was dissolved in a mixture of dimethylformamide (3mL) and water (0.75mL). To this solution, sodium acetate (143mg) and a solution of potassium cyanate (142mg) in water(1mL) were added successively at room temperature.

The mixtre was stirred overnight at 60°C, and was poured into a mixture of water and ethyl acetate. Aqueous layer was separated, the organic layer was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel eluting with dichloromethane and acetone to give the title compound (61.2mg).

^{1}H-NMR (DMSO-d_6) : δ 1.0-1.5(4H, m), 3.0-3.2(1H, m), 3.3-3.4(2H, m), 3.9(3H, s), 3.92-4.15(2H, m), 5.54(2H, s), 6.18(1H, t, J=5.6Hz), 6.94(1H, d, J=8.6Hz), 7.09(2H, d, J=8.9Hz), 7.56(2H, d, J=8.8Hz),

7.9(1H, dd, J=2.5,8.7Hz), 8.41(1H, d, J=2.3Hz).
MS (ESI) : 445.1 $(M+Na)^+$.

Example 299

N-(2-{4-[2-[(E)-Cyclopropyl(hydroxyimino)methyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (51.1mg) was obtained from N-(2-{4-[2-(cyclopropylcarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide obtained by Example 296 (60mg) in a manner similar to Example 289.

^{1}H-NMR (DMSO-d_6) : δ 0.8-1.1(2H, m), 1.4-1.5(2H, m), 2.4-2.5(1H, m), 2.95(3H, s), 3.3-3.4(2H, m), 3.88(3H, s), 4.08(1H, t, J=5.4Hz), 6.9(1H, d, J=8.6Hz), 7.06(2H, d, J=8.8Hz), 7.31(1H, t, J=5.8Hz), 7.48(2H, d, J=8.8Hz), 7.84(1H, dd, J=2.4,8.6Hz), 8.36(1H, d, J=2.4Hz).
MS (ESI) : 495.1 $(M+Na)^+$.

Example 300

N-(2-{4-[2-[(E)-Cyclopropyl(hydroxyimino)methyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (21.1mg) was obtained from N-(2-{4-[2-(cyclopropylcarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea obtained by Example 298 (45mg) in a manner similar to Example 289.

^{1}H-NMR (DMSO-d_6) : δ 0.8-1.1(2H, m), 1.3-1.5(2H, m), 2.4-2.5(1H, m), 3.88(3H, s), 3.9-4(2H, m), 5.54(2H, s), 6.18(1H, br-s), 6.9(1H, d, J=8.6Hz), 7.05(2H, d, J=8.5Hz), 7.47(2H, d, J=8.5Hz), 7.83(1H, dd, J=2.2,8.6Hz), 8.36(1H, d, J=2.2Hz).
MS (ESI) : 460.1 $(M+Na)^+$.

Example 301

S-1H-Tetrazol-5-yl (2-{4-[4-(6-methoxy-3-pyridinyl)-

2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)thiocarbamate

The title compound (51.1mg) was obtained from 4-nitrophenyl (2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)carbamate obtained by Example 245 (200mg) in a manner similar to Example 246.

Example 302

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]ethanone

The title compound (104mg) was obtained from 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-N-methoxy-4-(6-methoxy-3-pyridinyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 283 (300mg) and methyllithium (1.46mL) in a manner similar to Example 284.

^{1}H-NMR (DMSO-d_6) : δ 2.63(3H, s), 3.6-3.8(2H, m), 3.9(3H, s), 4-4.1(2H, m), 4.91(1H, t, J=5.5Hz), 6.94(1H, d, J=8.6Hz), 7.08(2H, d, J=8.8Hz), 7.53(2H, d, J=9.7Hz), 7.88(1H, dd, J=2.5,8.6Hz), 8.38(1H, d, J=2.4Hz).
MS (ESI) : 377.2 $(M+Na)^+$.

Example 303

4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenol

The title compound (311mg) was obtained from 5-{5-[4-(benzyloxy)phenyl]-2-[(2-pyridinylthio)methyl]-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 288 (570mg) in a manner similar to Example 287.

^{1}H-NMR (DMSO-d_6) : δ 3.86(3H, s), 4.68(2H, s), 6.7-6.9(3H, m), 7.1-7.2(1H, m), 7.28(2H, d, J=8.6Hz), 7.46(1H, d, J=8.1Hz), 7.6-7.8(2H, m), 8.31(1H, d, J=2.4Hz), 8.49(1H, dd, J=1,6.3Hz), 9.9(1H,

br-s).
MS (ESI) : 414.1(M+Na)$^+$.

Example 304

tert-Butyl [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate

The title compound (355mg) was obtained from 4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenol obtained by Example 303 (298mg) in a manner similar to Example 182.

^{1}H-NMR (DMSO-d_6) : δ 1.37(9H, s), 3.2-3.4(2H, m), 3.86(3H, s), 3.99(1H, t, J=5.7Hz), 4.69(2H, s), 6.87(1H, d, J=8.5Hz), 7(2H, d, J=8.7Hz), 7.1-7.3(1H, m), 7.4-7.5(3H, m), 7.7-7.85(2H, m), 8.31(1H, d, J=2.4Hz), 8.4-8.5(1H, m).
MS (ESI) : 557.2 (M+Na)$^+$.

Example 305

[2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine

The title compound (261mg) was obtained from tert-butyl [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]carbamate obtained by Example 304 (345mg) in a manner similar to Example 198.

^{1}H-NMR (DMSO-d_6) : δ 2.9(2H, t, J=5.6Hz), 3.86(3H, s), 3.97(2H, t, J=5.6Hz), 4.69(2H, s), 6.87(1H, d, J=8.7Hz), 7.01(2H, d, J=8.7Hz), 7.1-7.3(1H, m), 7.38(2H, d, J=8.6Hz), 7.46(1H, d, J=8Hz), 7.6-7.8(2H, m), 8.31(1H, d, J=2.2Hz), 8.49(1H, d, J=4.3Hz).
MS (ESI) : 435.1 (M+Na)$^+$.

Example 306

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]methanesulfonamide

The title compound (68.1mg) was obtained from [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine obtained by Example 305 (100mg) in a manner similar to Example 199.

MS (ESI) : 513.1 $(M+H)^+$.

Example 307

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]methanesulfonamide methanesulfonate

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]methanesulfonamide obtained by Example 306 (80mg) was dissolved in ethyl acetate (1mL) and cooled with ice. 0.1M methanesulfonic acid in ethyl acetate (1.57mL) was added to this solution.

The resulting precipitate was collected by filtraion, washed with ethyl acetate under a nitrogen stream, and dried in vacuo to give the title compound (48mg).

^{1}H-NMR (DMSO-d_6) : δ 2.37(3H, s), 2.95(3H, s), 3.33(2H, br-s), 3.87(3H, s), 4-4.1(2H, m), 4.7(2H, s), 6.87(1H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.1-7.2(1H, m), 7.4(2H, d, J=8.7Hz), 7.48(1H, d, J=8.1Hz), 7.6-7.8(2H, m), 8.31(1H, d, J=2.1Hz), 8.5(1H, d, J=4.2Hz).

Example 308

N-[2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]urea

The title compound (105mg) obtained from [2-(4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethyl]amine obtained by Example 305 (140mg) in

a manner similar to Example 200.

^{1}H-NMR (DMSO-d_6) : δ 3.86(3H, s), 3.98(2H, t, J=5.5Hz), 4.69(2H, s), 5.53(2H, s), 6.17(1H, t, J=5.6Hz), 6.87(1H, d, J=8.8Hz), 7.02(2H, d, J=8.8Hz), 7.1-7.2(1H, m), 7.39(2H, d, J=8.7Hz), 7.46(1H, d, J=8.1Hz), 7.6-7.8(2H, m), 8.31(1H, d, J=2.3Hz), 8.49(1H, dd, J=1,6.2Hz).

Example 309

2-Methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine

To a solution of 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazol-4-yl]pyridine obtained by Example 290-2 (505mg) in methanol (10 mL)-tetrahydrofuran (3.0mL), a solution of oxone (2.84g) in water (13.0mL) was added at 0℃.

After stirring for 10hrs at room temperature, the mixture was poured into ice cooling water. The product was extracted with ethyl acetate. The combined extracts were washed with saturated sodium hydrogencarbonate aqueous solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (547mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.41(3H, s), 3.86(3H, s), 3.97(3H, s), 6.79(1H, d, J=8Hz), 6.94(2H, d, J=9Hz), 7.56(2H, d, J=9Hz), 7.84(1H, dd, J=2.5,8.5Hz), 8.44(1H, d, J=2.5Hz)
MS (ESI) : 383 $(M+Na)^+$.

Example 310

5-[2-Isopropoxy-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

To a solution of 2-propanol (63.7µL) in dioxane (1.3mL), NaH and a solution of 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 (100mg) in dioxane (1.5mL) were

added at 0°C.

The mixture was refluxed for 10min, and poured into saturated ammonium chloride aqueous solution at 0°C. The product was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography to give the title compound (72.5mg).

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.47(6H, d, J=6.5Hz), 3.82(3H, s), 3.97(3H, s), 5.09-5.23(1H, m), 6.74(1H, d, J=8.5Hz), 6.87(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.82(1H, dd, J=2.3,9Hz), 8.44(1H, d, J=2.3Hz).
MS (ESI) : 341 $(M+H)^+$, 363 $(M+Na)^+$.

Example 311

2-Methoxy-5-[5-(4-methoxyphenyl)-2-(2,2,2-trifluoroethoxy)-1,3-oxazol-4-yl]pyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2,2,2-trifluoroethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.83(3H, s), 3.97(3H, s), 4.84(2H, q, J=8Hz), 6.75(1H, d, J=8Hz), 6.9(2H, d, J=6.5Hz), 7.44(2H, d, J=9Hz), 7.79(1H, dd, J=2.3,9Hz), 8.42(1H, d, J=2Hz)
MS (ESI) : 381 $(M+H)^+$, 403 $(M+Na)^+$.

Example 312

5-[2-(Cyclohexyloxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and cyclohexanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.47-2.09(10H, m), 3.82(3H, s), 3.97(3H, s), 4.8-5(1H, m), 6.74(1H, d, J=9Hz), 6.87(2H, d, J=8.5Hz), 7.42(2H, d, J=9Hz), 7.82(1H, dd, J=2.5,8.5Hz), 8.43(1H, d, J=2Hz).
MS (ESI) : 403 $(M+Na)^+$.

Example 313
5-[2-(Cyclopentyloxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and cyclopentanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.5-2.2(8H, m), 3.82(3H, s), 3.96(3H, s), 6.74(1H, d, J=9.5Hz), 6.87(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.82(1H, dd, J=2.3,8.5Hz), 8.43(1H, d, J=2.3Hz).
MS (ESI) : 367 $(M+H)^+$, 389$(M+N)^+$.

Example 314
5-[2-sec-Butoxy-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2-butanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.02(3H, t, J=7.5Hz), 1.44(3H, d, J=6Hz), 1.6-2(2H, m), 3.82(3H, s), 3.96(3H, s), 4.92-5.03(1H, m), 6.74(1H, d, J=8.5Hz), 6.87(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.82(1H, dd, J=2.5,8.5Hz), 8.43(1H, d, J=2.5Hz).
MS (ESI) : 355 $(M+H)^+$, 377 $(M+Na)^+$.

Example 315

2-(4-{4-(6-Methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenoxy)ethanol

The title compound (19.8mg) was obtained from 4-{4-(6-methoxy-3-pyridinyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-5-yl}phenol (90mg) obtained by Example 303 in a manner similar to Example 181.

^{1}H-NMR (DMSO-d_6) : δ 3.6-3.8(2H, m), 3.86(3H, s), 3.9-4.1(2H, m), 4.69(2H, s), 4.88(1H, br-s), 6.86(1H, d, J=8.6Hz), 7.01(2H, d, J=8.7Hz), 7.1-7.2(1H, m), 7.3-7.5(3H, m), 7.6-7.8(2H, m), 8.31(1H, d, J=2Hz), 8.5(1H, br-s).

MS (ESI) : 458.2 $(M+Na)^+$.

Example 316

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate

The title compound (241mg) was obtained from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol (200mg) in a manner similar to Example 285.

^{1}H-NMR (DMSO-d_6) : δ 2.38(3H, s), 3.8(3H, s), 3.88(3H, s), 4.2-4.4(2H, m), 6.89(1H, d, J=9.1Hz), 7.04(2H, d, J=8.9Hz), 7.4-7.8(3H, m), 8.35(1H, d, J=2.2Hz).

Example 317

2-Methoxy-5-{5-(4-methoxyphenyl)-2-[(4-pyridinylthio)methyl]-1,3-oxazol-4-yl}pyridine methanesulfonate

The title compound (37mg) was obtained from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate obtained by Example 316 (51mg) and 4-mercaptopyridine (29.1mg) in manners similar to Examples 286 and

307.

^{1}H-NMR (DMSO-d_6) : δ 2.33(3H, s), 3.79(3H, s), 3.87(3H, s), 4.92(2H, s), 6.88(1H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.44(2H, d, J=8.8Hz), 7.79(1H, dd, J=2.2,8.6Hz), 8.06(2H, d, J=6.7Hz), 8.34(1H, d, J=2.2Hz), 8.72(2H, d, J=6.7Hz).
MS (ESI) : 406.3 $(M+H)^+$.

Example 318
2-Methoxy-5-{5-(4-methoxyphenyl)-2-[(2-pyridinylthio)methyl]-1,3-oxazol-4-yl}pyridine methanesulfonate

The title compound (29.5mg) was obtained from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate obtained by Example 316 (51mg) and 2-mercaptopyridine (29.1mg) in manners similar to Examples 286 and 307.

^{1}H-NMR (DMSO-d_6) : δ 2.43(3H, s), 3.78(3H, s), 3.87(3H, s), 4.7(2H, s), 6.09(1H, br-s), 6.88(1H, d, J=8.5Hz), 7.01(2H, d, J=8.8Hz), 7.1-7.3(1H, m), 7.39(2H, d, J=8.9Hz), 7.5(1H, d, J=8.2Hz), 7.7-7.8(2H, m), 8.31(1H, d, J=2.3Hz), 8.51(1H, d, J=4.1Hz).
MS (ESI) : 428.2 $(M+Na)^+$.

Example 319
2-Methoxy-5-[5-(4-methoxyphenyl)-2-(2-propyn-1-yloxy)-1,3-oxazol-4-yl]pyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2-propyn-1-ol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.62(1H, t, J=2.3Hz), 3.83(3H, s), 3.97(3H, s), 5.07(2H, d, J=2.3Hz), 6.75(1H, d, J=8.5Hz), 6.89(2H, d, J=9Hz),

7.43(2H, d, J=9Hz), 7.8(1H, d, J=2.5Hz), 7.44(1H, d, J=2.5Hz).
MS (ESI) : 337 $(M+H)^+$, 359 $(M+Na)^+$.

Example 320

5-[2-(Cyclobutyloxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and cyclobutanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.6-2.5(6H, m), 3.82(3H, s), 3.99(3H, s), 5.1-5.22(1H, m), 6.73(1H, d, J=8.5Hz), 6.87(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.79(1H, dd, J=2,8.5Hz), 8.41(1H, d, J=2Hz).
MS (ESI) : 353 $(M+H)^+$, 375$(M+Na)^+$.

Example 321

5-[2-(Cyclopentylmethoxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and cyclopentylmethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.19-1.98(8H, m), 2.27-2.52(1H, m), 3.82(3H, s), 3.95(3H, s), 4.33(2H, d, J=7Hz), 6.74(1H, d, J=8.5Hz), 6.87(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.8(1H, dd, J=2.5,8.5Hz), 8.41(1H, d, J=2.5Hz).
MS (ESI) : 403 $(M+Na)^+$, 381 $(M+H)^+$.

Example 322

2-Methoxy-5-[2-(2-methoxyethoxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]pyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2-methoxyethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.45(3H, s), 3.75-3.83(2H, m), 3.82(3H, s), 3.98(3H, s), 4.57-4.64(2H, m), 6.76(1H, d, J=8.5Hz), 6.88(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.83(1H, dd, J=2.5,8.5Hz), 8.44(1H, d, J=2.5Hz).
MS (ESI) : 357 $(M+H)^+$, 379 $(M+Na)^+$.

Example 323
5-[2-(2-Fluoroethoxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2-fluoroethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 3.83(3H, s), 3.96(3H, s), 4.62-4.69(2H, m), 4.75-4.8(1H, m), 4.89-4.94(1H, m), 6.74(1H, d, J=8Hz), 6.89(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.79(1H, dd, J=2.3,8Hz), 8.41(1H, d, J=2.3Hz).
MS (ESI) : 345 $(M+H)^+$, 367 $(M+Na)^+$.

Example 324
5-[2-(ethylthio)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.49(3H, t, J=7.4Hz), 3.24(2H, q, J=7.4Hz), 3.83(3H, s), 3.96(3H, s), 6.75(1H, d, J=8.5Hz), 6.9(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.82(1H, dd, J=2,8.5Hz), 8.44(1H, d, J=2Hz).
MS (ESI) : 343 $(M+H)^+$, 365 $(M+Na)^+$.

Example 325

5-[2-(Cyclopropylmethoxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and cyclopropylmethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 0.36-0.47(2H, m), 0.63-0.73(2H, m), 1.26-1.48(1H, m), 3.82(3H, s), 3.95(3H, s), 4.29(2H, d, J=7Hz), 6.73(1H, d, J=8.5Hz), 6.87(2H, d, J=6.5Hz), 7.43(2H, d, J=9Hz), 7.79(1H, dd, J=2.3,8.5Hz), 8.41(1H, d, J=2.5Hz).
MS (ESI) : 353 $(M+H)^+$.

Example 326

2-Methoxy-5-{5-(4-methoxyphenyl)-2-[(1H-tetrazol-5-ylthio)methyl]-1,3-oxazol-4-yl}pyridine

The title compound (21.2mg) was obtained from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl methanesulfonate obtained by Example 316 (51mg) and 2-mercaptotetrazole (26.7mg) in a manner similar to Example 286.

^{1}H-NMR (DMSO-d_6) : δ 3.79(3H, s), 3.87(3H, s), 4.41(2H, s), 6.86(1H, d, J=8.6Hz), 7.01(2H, d, J=8.8Hz), 7.4(2H, d, J=8.8Hz), 7.8(1H, dd, J=1.8,9.9Hz), 8.31(1H, d, J=2.1Hz).
MS (ESI) : 395.2 $(M-H)^-$.

Example 327

5-[2-(2-Ethoxyethoxy)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound was obtained from 2-methoxy-5-[5-(4-methoxyphenyl)-2-(methylsulfonyl)-1,3-oxazol-4-yl]pyridine obtained by Example 309 and 2-ethoxyethanol in a manner similar to Example 310.

^{1}H-NMR (200MHz, $CDCl_3$) : δ 1.25(3H, t, J=7Hz), 3.6(2H, q, J=7Hz), 3.78-3.85(2H, m), 3.82(3H, s), 3.95(3H, s), 4.58-4.62(2H, m), 6.74(1H, d, J=8.5Hz), 6.87(2H, d, J=9Hz), 7.42(2H, d, J=8.5Hz), 7.79(1H, dd, J=2.3,9Hz), 8.41(1H, d, J=2.3Hz).

MS (ESI) : 393$(M+Na)^+$.

Example 328

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(methylthio)-1,3-oxazole

The title compound was obtained from 5-[4-(benzyloxy)phenyl]-2-chloro-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 167-3 in a manner similar to Example 157.

^{1}H-NMR ($CDCl_3$) : δ 2.71(3H, s), 3.83(3H, s), 5.08(2H, s), 6.70-7.70(13H, m).

MS (ESI) : 404.2 $(M+H)^+$.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats

was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μL of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
12	3.2	>1.5
33	3.2	>1.5
54	3.2	>1.5
55	3.2	>1.5
118	3.2	>1.5
122	3.2	>1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μL Aliquots of human whole blood were immediately incubated with 2μL of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37°C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μL of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4°C to obtain serum. A 100μL aliquot of serum was mixed with 400μL methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μL aliquots of human whole blood were incubated with either 2μL dimethyl sulfoxide vehicle or 2μL of a test compound at final concentrations for 15 min at 37°C. This was followed by incubation of the blood with 10μL of 5mg/mL lipopolysaccharide for 24hrs at 37°C for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000×g for 5 min at 4°C to obtain plasma. A 100μL aliquot of plasma was mixed with 400μL methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000

×g for 5min at 4°C and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
12	< 0.01	> 0.1
33	< 0.01	> 0.1
54	< 0.01	> 0.1
55	< 0.01	> 0.1
118	< 0.01	> 0.1
122	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least 7days prior to blood collection.

Platelet-rich plasma was obtained from the supernatant fraction of blood after centrifugation at 1200rpm. for 10min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000rpm for 10min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2min at 37°C after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist-induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

As shown above, the object compound (I) or pharmaceutically

acceptable salts thereof of this invention possesses COX inhibiting activity, especially COX-I inhibiting activity, and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago; inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.]; inflammatory eye condition [e.g. conjunctivitis, etc.]; lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.]; condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varioloid, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia; inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc.] ; pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for

cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage(e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc..

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc..

The Compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting cyclooxygenase, especially cyclooxygenase I. Therefore, the Compound (I) or pharmaceutically acceptable salts thereof are useful for treating and/or preventing diseases, more particularly useful for treating and/or preventing inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases in human beings or animals.

This application is based on Australian Provisional Patent Application No.2003900207 filed on January 17, 2003 and No.2003901873 filed on March 31, 2003, the contents of which are hereby incorporated by references.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.